Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 04-108715

54. **TÍTULO** Benz-Azoles sustituidos y su aplicación como inhibidores Quinasa PAF

51. **CLASIFICACIÓN INTERNACIONAL** A61K 31/41, C07D 401/12. 405/14, 401/14, 417/12, 417/14, 413/14, 409/14, 413/12, 471/08. A61P 35/00

71. **SOLICITANTE** Chiron Corporation

DOMICILIO California, Estados Unidos.

74. **APODERADO** Dilia María Rodríguez D'Alemán

22. **BOGOTÁ, D. C.,** oct 28, 04

(FORMA P-10)

1

PETITORIO

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04108715 00000000 Folios: 446
Fecha (AMD): 2004-10-20 16:40:27
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☐ Capitulo I. ☒ Capitulo II.

2) SOLICITANTE (71)	**Nombre: CHIRON CORPORATION** **Dirección: 4560 Horton Street, Emeryville, CA 94608-2916, Estados Unidos** **Nacionalidad o domicilio: Emeryville, California, Estados Unidos** **Lugar de constitución: Delaware, Estados Unidos**	**IDENTIFICACIÓN** **C.C.** ☐ **NIT:** ☒ **C.E.** ☐ **OTRO** ☐ **Cual** _____ **NÚMERO** _____
	Teléfono: **Fax:** **E. Mail:**	
3) REPRESENTANTE O APODERADO	**Nombre:** DILIA MARÍA RODRÍGUEZ D´ALEMAN **Dirección:** Carrera 11 N°. 93-43 Of. 404 Santafé de Bogotá D.C. **Teléfono:** 6350835 **Fax:** 6350824 **E. Mail:** clarkemodet@clarkemodet.com.co	**IDENTIFICACIÓN** **C.C.** ☒ **NIT:** ☐ **C.E.** ☐ **OTRO** ☐ **NÚMERO:** 41.654.882 **TP:** 20824 CSJ
4) INVENTOR (ES) (72)	**Nombre: 1. RENHOWE, Paul, A.; 2. RAMURTHY, Savithri; 3. AMIRI, Payman; 4. LEVINE, Barry, Haskell; 5. POON, Daniel, J. 6. SUBRAMANIAN, Sharadha; 6. SUNG, Leonard; 7. FANTL, Wendy** **Dirección: 1. 262 Stetson Drive, Danville, CA 94506, USA; 2. 1151 Maggie Lane, Walnut Creek, CA 94597 USA; 3. 1025 Lizann Drive, Lafayette, CA 94549 USA; 4. 1142 Brown Avenue, Lafayette, CA 94549 USA; 5. 415 Langunitas Avenue, Apt. 103, Oakland, CA 94610 USA; 6. 118 Amherst Court, Irvine CA 92612 92612 USA; 7. 35 Hancock Street, San Francisco, CA 94114 USA** **Nacionalidad o Domicilio: Todos los anteriores estadounidenses**	

5) PCT (86)
Solicitud Internacional No. PCT/US03/10117 Fecha: Marzo 31, 2003
Publicación Internacional No. WO 03/082272 A1 Fecha: Octubre 9, 2003

6)Titul (54): BENZAZOLES SUSTITUIDOS Y SU APLICACIÓN COMO INHIBIDORES QUINAZA RAF

7) Clasificación Internacional: A 61K 31/41, CO7D 401/12, 405/14, 401/14, 417/12, 417/14, 413/14, 407/14, 413/12, 471/08, A61P 35/00

8) PRI RIDAD	**33) País de Origen**	**(32) Fecha**	**(31) Número de Solicitud**
SI ☒ **NO** ☐	**ESTADOS UNIDOS**	**MARZO 29, 2002**	**60/369,066**

9) C mprobante de pag N°. 04-79,735 Fecha: Octubre 12, 2004

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04108715 00000000 Folios: 446
Fecha (AMD): 2004-10-26 16:40:37
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAR
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 79,735
FECHA : OCTUBRE 12 DE 2004

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	23291510	11/10/2004	5,951,000.00

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	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

P586

10) ANEX S

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Comprobante de pago por reivindicación de prioridad
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- [x] Poderes, si fuera el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12 y 6 x 6 cm
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- [x] Otros:
  1. PCT Capítulo II
  2. Hoja de cálculo
  3. Reporte internacional de búsqueda
  4. Solicitud PCT

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA: _____

C.C. 41.654.882 de Bogota TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

TRADUCCIÓN OFICIAL No. 03/104 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido de conformidad con el Certificado de Idoneidad Profesional No. 0045 expedido por la Universidad Nacional de Colombia.

(Se traducen un Poder otorgado por Chiron Corporation, un Certificado Notarial y la Apostilla No. 152057, todo escrito en inglés).

CLARKE, MODET & CO. COLOMBIA

PODER

Yo (Nosotros) el (los) suscrito(s), representante(s) legal(es) de Chiron Corporation, sociedad organizada y existente bajo las leyes de Delaware y en desempeño en la actualidad de su actividad comercial, domiciliada en 4560 Horton Street, Emeryville, CA, 94608, EE.UU., por el presente otorgamos Poder a DILIA MARÍA RODRÍGUEZ D'ALEMÁN, identificada con cédula de ciudadanía No. 41.654.882 de Bogotá y Tarjeta Profesional 20824 y CLAUDIA LUCIA CARO RAMIREZ, identificada con Tarjeta Profesional 36448 y cédula de ciudadanía No 40.017.374 de Tunja, con domicilio en Santafé de Bogotá, Colombia, para que actuando en su orden en nombre de la otorgante la representen ante cualquier entidad, autoridad y/o persona, especialmente ante

TRADUCCIÓN OFICIAL No. 03/104
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTÉRPRETE OFICIAL
C. IDONEIDAD 045
UNIVERSIDAD NACIONAL DE COLOMBIA

Esta copia corresponde en el original a la vista.
Bogotá, D.C.
28 OCT 2004
AGUSTIN MORALES RIVERA
NOTARIO CUARENTA Y UNO

las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

1) Solicitar, tramitar, obtener y/o registrar cualesquiera de las modalidades de Propiedad Industrial, tales como: Patentes de Invención, Modelos de Utilidad; Diseños Industriales, variedades vegetales, Marcas, Lemas, Nombres y Enseñas Comerciales y Denominaciones de Origen; así como sus renovaciones, prórrogas, traspasos, cambios de nombre y/o domicilio, contratos y licencias.

2) Solicitar, tramitar, obtener, y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how o crédito mercantil.

3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, cesiones, traspasos, cambios de nombre y/o domicilio, contratos y licencias.

4) Ejercer acciones de oposición, observación, reclamos, reivindicaciones, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrán intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía, acciones

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TRADUCTOR E INTERPRETE OFICIAL
C. IDONEIDAD 045
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Es copia fiel y exacta tomada de su original que tuve a la vista.
28 OCT 2004
AGUSTIN MORALES RIVERA
NOTARIO CUARENTA Y UNO

o juicios promovidos por el mandante o contra él.

5) Registrar nombres de dominio ante la entidad competente.

6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, aceptar cláusulas compromisorias, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir derechos concedidos o en curso de concesión, admitir los hechos del proceso.

7) Ratificar o no la agencia oficiosa.

8) Así mismo facultamos a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en Chiron Corporation, Emeryville, CA, hoy día 19 de Marzo, 2003.

Por: (Firmado) Steven W. Collier

Secretario Asistente

Chiron Corporation

CERTIFICADO NOTARIAL (Cuando el solicitante es una SOCIEDAD)

(Poderes otorgados en El Salvador, México, Estados Unidos de América y Venezuela)

El suscrito Notario CERTIFICA que:

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 OCT 2004
AGUSTIN MORALES RIVERA
NOTARIO CUARENTA Y UNO

TRADUCCION OFICIAL File
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
C. IDONEIDAD 045
UNIVERSIDAD NACIONAL DE COLOMBIA

1). Steven W. Collier, (nombre de quien firma el poder), mayor de edad y domiciliado en Oakland CA, ,suscribió el anterior documento.

2) El otorgante le es conocido personalmente y tiene capacidad para firmar el documento.

3) El otorgante ha suscrito el anterior documento en su calidad de Secretario Asistente de la persona jurídica Chiron Corporation.

4) La mencionada persona jurídica con domicilio comercial en Emeryville CA, está debidamente constituida, tiene actualmente existencia legal y el fin para el cual se otorga este poder se encuentra dentro de su objeto social.

5) El otorgante tiene en efecto la capacidad referida y su representación es legal y está autorizado para otorgar este poder.

6) Fundamento las certificaciones 3), 4) y 5) en los documentos auténticos que para tal fin me fueron exhibidos.

(Firmado) Elissa M. Nash

Notario Público

(Sello Notarial a Tinta: Elissa M. Nash, Comisión No. 1262878, Notario Público, California, Condado de Alameda, Mi Comisión Vence Mayo 10, 2004)

Nota: El Consulado de Colombia debe autenticar la firma del Notario Público.

Para todos los demás países el Señor Cónsul de Colombia ante quien se

n 3 / 1 0 4
TRADUCCION OFICIAL No.
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
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28 OCT 2004
AGUSTIN MORALES RIVERA
NOTARIO CUARENTA Y UNO

otorgue, debe expedir una certificación dejando constancia de: 1) la existencia legal de la sociedad, 2) que cumple actualmente con su objeto social, y 3) que la persona o personas que otorgan este poder están facultadas para hacerlo. El Cónsul también certificará que los tuvo a la vista los documentos que prueban y acreditan tales circunstancias.

Estado de California

(Sello Pre-Impreso)

SECRETARIO DE ESTADO

APOSTILLA

(Convención de La Haya de Octubre 5 1961)

1. *País: Estados Unidos de América*

   Este documento público

2. *Ha sido firmado por Elissa M. Nash*

3. *Actuando en calidad de Notario Público, Estado de California*

4. *Lleva el sello/estampilla de Elissa M. Nash, Notario Público, Estado de California*

CERTIFICADO

5. *En Sacramento*

6. *El 11 de Abril del 2003*

7. *Por el Sub-Secretario de Estado, Estado de Ca[illegible]*

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 OCT 2004
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

TRADUCCION OFICIAL No 03/104
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
C. IDONEIDAD 045
UNIVERSIDAD NACIONAL DE COLOMBIA

8.	*No. 152057*
9.	*Sello/Estamplilla*
(Sello de Oblea del Estado de California, Sello a tinta del Secretario de Estado)	
(Sello Redondo a Tinta del Secretario de Estado)	
10.	*Firma (Firmado)*
	Kevin Shelley
	Secretario de Estado
	Por (Firmado) Ilegible
NP-24 A (Rev 1-03)	osp 03 74700

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Bogotá, Mayo 27, 2003.

03 / 1

TRADUCCION OFICIAL No. _____
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
C. IDONEIDAD 045
UNIVERSIDAD NACIONAL DE COLOMBIA

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 OCT 2004
AGUSTIN MORALES RIVERA
NOTARIO CUARENTA Y UNO


AGUSTIN GONZALEZ RIVERA
NOTARIO CUARENTA Y UNO
28 OCT 2004
que lleva a la vista.

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by Elissa M. Nash*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of Elissa M. Nash, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 11th day of April 2003*
7. *by Deputy Secretary of State, State of California*
8. *No. 152057*
9. *Seal/Stamp:*



10. *Signature*

KEVIN SHELLEY
Secretary of State

BY _____

Esta copia coincide con el que tuve a la vista
Bogotá, D.C.
29 OCT 2004
AGUSTIN MORALES RIVERA
NOTARIO CUARENTA Y UNO

OFFICE OF THE SECRETARY OF STATE

NP-24 A (REV. 1-03)

OSP 03 74709

AGUILERA

...E ORIGINAL

...ADO 045

...ONAL DE COLOMBIA

JUAN P...

2004 OCT ...

Esta copia coincide con el original que tuve a la vista.

NOTARIO CUARENTA Y UNO
AGUSTIN AGUILERA

COLOMBIA

PODER

Yo (nosotros), abajo firmante(s)

en mi (nuestro) carácter de representante(s) legales de

una sociedad organizada y existente de acuerdo con las leyes de

y en actual cumplimiento de su objeto social, con domicilio en

por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.
3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
4) Ejercer acciones de oposición, observación, reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).
5) Registrar nombres de dominio ante la entidad competente.
6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.
7) Ratificar o no la agencia oficiosa.
8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los días de

TRADUCCION OFICIAL
JUAN PABLO PIEDRAHITA AGUILERA
INTERPRETE OFICIAL
UNIVERSIDAD NACIONAL DE COLOMBIA

POWER OF ATTORNEY

I (we), the undersigned

Legal representative(s) of Chiron Corporation

An organiztion existing under the laws of Delaware

And in present execution of its business activity, domiciled at
4560 Horton Street, Emeryville, CA 94608, US

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, assignments, changes of name and/or domicile, agreements and licenses.
2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.
3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or assignments, changes of name and/or domicile, agreements and licenses.
4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the above- mentioned matters and against the unfair competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.
5) To register domain names before the competent entity.
6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related objet and waive or renounce the rights granted or in process of granting, admit the facts of the case.
7) To ratify or not the officious agency.
8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extrajudicial attorneys, substitute this Power of Attorney and to revoke such sustitutions.

Granted and signed at Chiron Corporation Emeryville, CA

on this 19th day of March 2003

Firma / signatura Steven W.
Assistant Secretary
Chiron Corporation

Esta copia coincide con el original que tuve a la vista.
28 OCT 2004
AGUSTIN MORALES RIVERA

CERTIFICADO NOTARIAL

(Cuando el solicitante es SOCIEDAD)

(Poderes otorgados en: El Salvador, Estados Unidos, México y Venezuela)

A los días del mes de de , el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado _____ _____ firmó de su puño y letra el documento que antecede.

2. Conozco al (a la) otorgante y que este (a) está legalmente capacitado para el otorgamiento.

3. El otorgante ha firmado el referido documento en su carácter de _____ de la persona jurídica _____

4. La referida persona jurídica con sede en _____ está legalmente constituida y que tiene actualmente existencia legal y que el acto para el cual se ha otorgado este poder está comprendido entre los que constituyen su objeto social.

5. El otorgante tiene efectivamente la representación que ostenta, que esta es legítima y que está facultado para otorgar este poder.

6. Las anteriores certificaciones de los puntos 3, 4 y 5, me constan porque he tenido a la vista los documentos auténticos.

_____
Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

CERTIFICADO NOTARIAL (Cuando el solicitante es INDIVIDUO)

A los días del mes de de , el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____ _____ firmó en su presencia el documento que antecede, conoce al otorgante y que este está legalmente capacitado para el otorgamiento.

_____
Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

Para todos los demás países el Señor Cónsul de Colombia o ante quien se otorgue debe expedir una certificación dejando constancia 1) de la existencia legal de la sociedad, 2) de que este ejerce actualmente el objeto social, y 3) de que la persona o personas que otorgan poder están facultadas para hacerlo, dejando constancia además de que tuvo a la vista las pruebas que acrediten tales circunstancias.

LEGALIZACION POR EL CONSUL DE COLOMBIA

OCT 2004

NOTARIAL CERTIFICATE

(When the applicant is a CORPORATION)

(Powers of attorney granted in: El Salvador, Mexico, U.S.A. and Venezuela)

This day of
The undersigned Notary CERTIFIES that:

1. Steven W. Collier
(name of the person who signs the power of attorney)

of legal age and domiciled in Oakland, CA set his hand on the foregoing document.

2. The grantor is to him personally known and that he/she has legal capacity to execute the document.

3. The grantor has executed the foregoing document in his capacity of Assistant Secretary of the juridical person Chiron Corporation

4. The mentioned juridical person with place of business in Emeryville, CA is duly organized, has actual legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. The grantor has in fact the referred quality and that his/her representation is legal and that he/she is empowered to grant this power of attorney.

6. I have based the above certifications 3, 4 and 5, on the authentic documents which for such purpose were exhibited to me.

Notary Public
Elissa M. Nash

NOTA: Then the Colombian Consul must legalize the signature of the Notary Public.

ELISSA M. NASH
Commission # 1325509
Notary Public - California
Alameda County
My Comm. Expires May 10, 2004

NOTARIAL CERTIFICATE (When the applicant is a INDIVIDUALS)

On this day of
The undersigned Notary CERTIFIES that:

1. _____
(name of the person who signs the Power of Attorney)

of legal age and domiciled at _____ _____ signed in his presence the foregoing document, the grantor is to him personally known and that he/she has legal capacity to execute the document.

_____
Notary Public

NOTA: Then the Colombian Consul must legalize the signature of the Notary Public.

For all other countries the Colombian Consul or before who it is granted must issue a certification stating 1) the legal existence of the corporation, 2) that the corporate purposes are actually being accomplished , 3) that the person or persons who grant this Power of Attorney are empowered to do it. The Consul will certify also that the documents evidencing those circumstances were exhibited to him.

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JUAN PABLO PIEDRAHITA AGUILERA
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UNIVERSIDAD NACIONAL DE COLOMBIA

P.586

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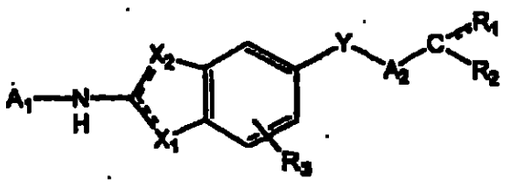
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WO 03/082272 A1

(54) Title: SUBSTITUTED BENZAZOLES AND USE THEREOF AS RAF KINASE INHIBITORS



(I)

(57) Abstract: New substituted benz-azole compounds of formula (I), compositions and methods of inhibition of Raf kinase activity in a human or animal subject are provided. The new compounds compositions may be used either alone or in combination with at least one additional agent for the treatment of a Raf kinase mediated disorder, such as cancer.

SUBSTITUTED BENZAZOLES AND USE THEREOF AS RAF KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to new substituted benz-azole-like compounds and pharmaceutically acceptable salts, esters or prodrugs thereof, compositions of the new compounds together with pharmaceutically acceptable carriers, and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of cancer.

BACKGROUND OF THE INVENTION

The Raf serine/threonine kinases are essential components of the Ras/Mitogen-Activated Protein Kinase (MAPK) signaling module that controls a complex transcriptional program in response to external cellular stimuli. Raf genes code for highly conserved serine-threonine-specific protein kinases which are known to bind to the ras oncogene. They are part of a signal transduction pathway believed to consist of receptor tyrosine kinases, p21 ras, Raf protein kinases, Mek1 (ERK activator or MAPKK) kinases and ERK (MAPK) kinases, which ultimately phosphorylate transcription factors. In this pathway Raf kinases are activated by Ras and phosphorylate and activate two isoforms of Mitogen-Activated Protein Kinase Kinase (called Mek1 and Mek2), that are dual specificity threonine/tyrosine kinases. Both Mek isoforms activate Mitogen Activated Kinases 1 and 2 (MAPK, also called Extracellular Ligand Regulated Kinase 1 and 2 or Erk1 and Erk2). The MAPKs phosphorylate many substrates including transcription factors and in so doing set up their transcriptional program. Raf kinase participation in the Ras/MAPK pathway influences and regulates many cellular functions such as proliferation, differentiation, survival, oncogenic transformation and apoptosis.

Both the essential role and the position of Raf in many signaling pathways have been demonstrated from studies using deregulated and dominant inhibitory Raf mutants in mammalian cells as well as from studies employing biochemical and genetic

techniques model organisms. In many cases, the activation of Raf by receptors that stimulate cellular tyrosine phosphorylation is dependent on the activity of Ras, indicating that Ras functions upstream of Raf. Upon activation, Raf-1 then phosphorylates and activates Mek1, resulting in the propagation of the signal to downstream effectors, such as MAPK (mitogen-activated protein kinase) (Crews et al. (1993) *Cell* 74:215). The Raf serine/threonine kinases are considered to be the primary Ras effectors involved in the proliferation of animal cells (Avruch et al. (1994) *Trends Biochem. Sci.* 19:279).

Raf kinase has three distinct isoforms, Raf-1 (c-Raf), A-Raf, and B-Raf, distinguished by their ability to interact with Ras, to activate MAPK kinase pathway, tissue distribution and sub-cellular localization (Marias et. Al., *Biochem. J.* 351: 289-305, 2000; Weber et. al., *Oncogene* 19:169-176, 2000; Pritchard et. al., *Mol. Cell. Biol.* 15:6430-6442, 1995). Raf kinases are activated by Ras and phosphorylate and activate two isoforms of Mitogen-Activated Protein Kinase Kinase (called Mek1 and Mek2) that are dual specificity threonine/tyrosine kinases. Both Mek isoforms activate Mitogen Activated Kinases 1 and 2 (MAPK, also called Extracellular Ligand Regulated Kinase 1 and 2 or Erk1 and Erk2). The MAPKs phosphorylate many substrates including cytosolic proteins and ETS family of transcription factors. Raf kinase participation in the Ras/MAPK pathway influences and regulates many cellular functions such as proliferation, differentiation, survival, cell cycle progression and apoptosis.

Activating mutation of one of the Ras genes can be seen in ~20% of all tumors and the Raf/MEK/ERK pathway is activated in ~30% of all tumors (Bos et. al., *Cancer Res.* 49:4682-4689, 1989) (Hoshino et. al., *Oncogene* 18:813-822, 1999). Recent studies have shown that B-Raf mutation in the skin nevi is a critical step in the initiation of melanocytic neoplasia (Pollock et. al., *Nature Genetics* 25: 1-2, 2002). Furthermore, most recent studies have emerged that activating mutation in the kinase domain of B-Raf occurs in ~66% of melanomas, 12% of colon carcinoma and 14% of liver cancer (Davies et. al., *Nature* 417:949-954, 2002) (Yuen et. al., *Cancer Research* 62:6451-6455, 2002) (Brose et. al., *Cancer Research* 62:6997-7000, 2002).

Inhibitors of Raf/MEK/ERK pathway at the level of Raf kinases can potentially be effective as therapeutic agents against tumors with over-expressed or mutated receptor tyrosine kinases, activated intracellular tyrosine kinases, tumors with aberrantly expressed Grb2 (an adapter protein that allows stimulation of Ras by the Sos exchange factor) as well as tumors harboring activating mutations of Raf itself. In the early clinical

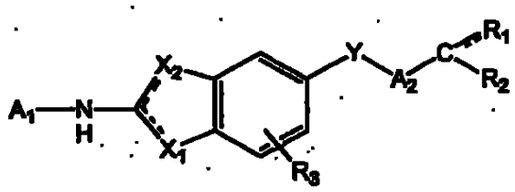
trails inhibitor of Raf-1 kinase that also inhibit B-Raf have shown promise as therapeutic agents in cancer therapy (Crump, *Current Pharmaceutical Design* 8: 2243-2248, 2002; Sebastien et. al., *Current Pharmaceutical Design* 8: 2249-2253, 2002).

Disruption of Raf expression in cell lines through the application of RNA antisense technology has been shown to suppress both Ras and Raf-mediated tumorigenicity (Kolch et al., *Nature* 349:416-428, 1991; Monia et al., *Nature Medicine* 2(6):668-675, 1996).

Several Raf kinase inhibitors have been described as exhibiting efficacy in inhibiting tumor cell proliferation in *vitro* and/or *in vivo* assays (see, *e.g.*, U.S. Pat. Nos. 6,391,636, 6,358,932, 6,037,136, 5,717,100, 6,458,813, 6,204,467, and 6,268,391). Other patents and patent applications suggest the use of Raf kinase inhibitors for treating leukemia (see, *e.g.*, U.S. Patent Nos. 6,268,391, and 6,204,467, and published U.S. Patent Application Nos. 20020137774; 20020082192; 20010016194; and 20010006975), or for treating breast cancer (see, *e.g.*, U.S. Patent Nos. 6,358,932, 5,717,100, 6,458,813, 6,268,391, and 6,204,467, and published U.S. Patent Application No. 20010014679).

SUMMARY OF THE INVENTION

New substituted benz-azole compounds and pharmaceutically acceptable salts thereof or esters having a solubility enhancing moieties or prodrugs thereof are provided of the formula (I):



(I)

wherein, X_1 and X_2 are independently selected from =N-, -NR_4-, -O- or –S-, provided that if X_1 is -NR_4-, -O- or –S-, then X_2 is =N-, or if X_2 is -NR_4-, -O- or –S-, then X_2 is =N-, and both X_1 and X_2 are not =N-;

Y is O or S;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl,

heteroarylheteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, biarylalkyl, or heteroarylarylalkyl;

A_2 is substituted or unsubstituted heteroaryl;

R_1 is O or H, and R_2 is NR_5 R_6 or hydroxyl; or R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group; wherein, the dashed line represents a single or double bond;

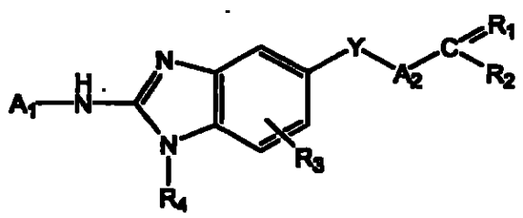
R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen, hydroxyl, alkylamino, dialkylamino or alkyl;

R_5 and R_6 are independently selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl; or R_5 and R_6 are taken together to form substituted or unsubstituted heterocyclo or heteroaryl; and

the pharmaceutically acceptable salts, esters and prodrugs thereof.

In other embodiments, new substituted benz-azole compounds are provided of the formula (II):

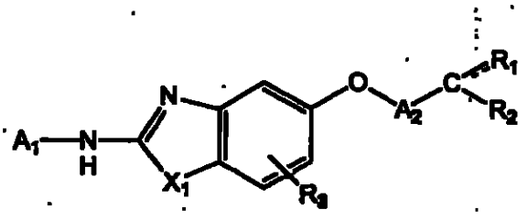


(II)

wherein and Y, Ar_1, Ar_2, R_1, R_2, R_3 and R_4 are as defined above; and

the pharmaceutically acceptable salts, esters, and prodrugs thereof.

In other embodiments, new substituted benz-azole compounds are provided of the formula (III):

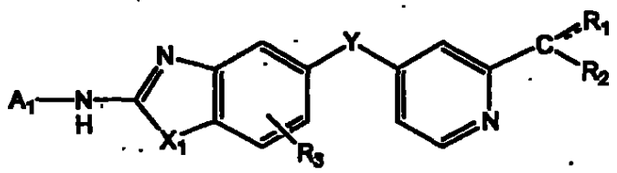


(III)

wherein X_1, Ar_1, Ar_2, R_1, R_2 and R_3 are as defined above; and

the pharmaceutically acceptable salts, esters, tautomers and prodrugs thereof.

In other embodiments, new substituted benz-azole compounds are provided of the formula (IV):

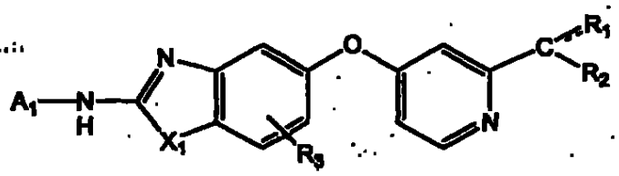


(IV)

wherein X_1, Y, Ar_1, R_1, R_2 and R_3 are as defined above; and

the pharmaceutically acceptable salts, esters, tautomers and prodrugs thereof.

In yet other embodiments, new substituted benz-azole compounds are provided of the formula (V):



(V)

wherein X_1, Ar_1, R_1, R_2 and R_3 are as defined above; and

the pharmaceutically acceptable salts, esters, tautomers and prodrugs thereof.

In other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV) or (V) effective to reduce or prevent tumor growth in the subject.

In yet other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV) or (V) effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer.

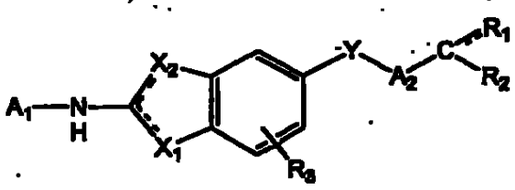
In yet other aspects, the present invention provides therapeutic compositions comprising at least one compound of formula (I), (II), (III), (IV) or (V) in combination with one or more additional agents for the treatment of cancer, as are commonly employed in cancer therapy.

The compounds of the invention are useful in the treatment of cancers, including carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) and adenomas (e.g., villous colon adenoma).

The invention further provides compositions, methods of use, and methods of manufacture as described in the detailed description of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In accordance with one aspect of the present invention, new substituted benz-azole compounds and pharmaceutically acceptable salts, esters or prodrugs thereof are provided of the formula (I):



(I)

wherein, X_1 and X_2 are independently selected from =N-, -NR_4-, -O- or –S-, provided that if X_1 is -NR_4-, -O- or –S-, then X_2 is =N-, or if X_2 is -NR_4-, -O- or –S-, then X_2 is =N-, and both X_1 and X_2 are not =N-; Y is O or S;

Y is O or S;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, heteroarylheteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, biarylalkyl, or heteroarylarylalkyl;

A_2 is substituted or unsubstituted heteroaryl;

R_1 is O or H, and R_2 is NR_5 R_6 or hydroxyl; or R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group; wherein, the dashed line represents a single or double bond;

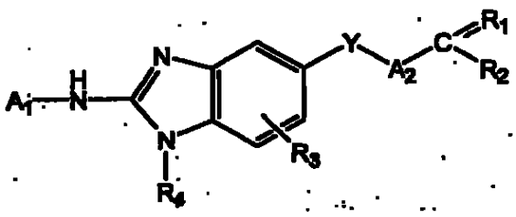
R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen, hydroxyl, alkylamino, dialkylamino or alkyl;

R_5 and R_6 are independently selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl; or R_5 and R_6 are taken together to form substituted or unsubstituted heterocyclo or heteroaryl; and

the pharmaceutically acceptable salts, esters and prodrugs thereof.

In other embodiments, new substituted benz-azole compounds are provided of the formula (II):

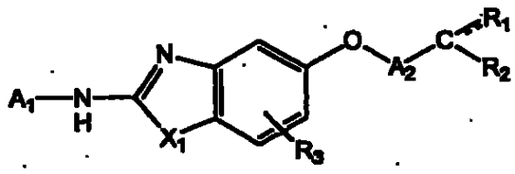


(II)

wherein and Y, Ar_1, Ar_2, R_1, R_2, R_3 and R_4 are as defined above; and

the pharmaceutically acceptable salts, esters, and prodrugs thereof.

In other embodiments, new substituted benz-azole compounds are provided of the formula (III):

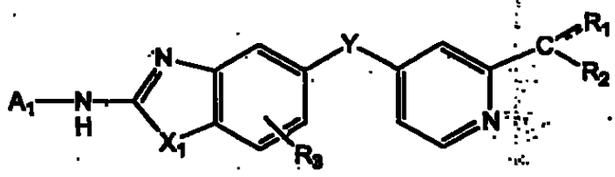


(III)

wherein X_1, Ar_1, Ar_2, R_1, R_2 and R_3 are as defined above; and

the pharmaceutically acceptable salts, esters, tautomers and prodrugs thereof.

In other embodiments, new substituted benz-azole compounds are provided of the formula (IV):

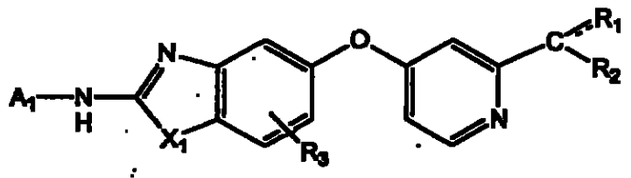


(IV)

wherein X_1, Y, Ar_1, R_1, R_2 and R_3 are as defined above; and

the pharmaceutically acceptable salts, esters, tautomers and prodrugs thereof.

In yet other embodiments, new substituted benz-azole compounds are provided of the formula (V):



(V)

wherein X_1, Ar_1, R_1, R_2 and R_3 are as defined above; and

the pharmaceutically acceptable salts, esters, tautomers and prodrugs thereof.

In another aspect, the present invention provides methods of treating human or animal subjects suffering from a Raf related disorder, such as cancer. Thus, the present invention provides methods of treating a human or animal subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula I, II, III, IV or V above, either alone or in combination with other anticancer agents.

In other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV) or (V) effective to reduce or prevent tumor growth in the subject.

In yet other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV) or (V) effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer. A number of suitable anticancer agents to be used as combination therapeutics are contemplated for use in the methods of the present invention. Indeed, the present invention contemplates, but is not limited to, administration of numerous anticancer agents such as: agents that induce apoptosis; polynucleotides (e.g., ribozymes); polypeptides (e.g., enzymes); drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers (e.g. interferons [e.g. IFN-a, etc.] and

interleukins [e.g. IL-2, etc.], etc.); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g. all-trans-retinoic acid, etc.); gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; inhibitors of angiogenesis, and the like. Numerous other examples of chemotherapeutic compounds and anticancer therapies suitable for coadministration with the disclosed compounds of formula (I), (II), (III), (IV) or (V) are known to those skilled in the art.

In preferred embodiments, anticancer agents to be used in combination with compounds of the present invention comprise agents that induce or stimulate apoptosis. Agents that induce apoptosis include, but are not limited to, radiation (e.g., W); kinase inhibitors (e.g., Epidermal Growth Factor Receptor [EGFR] kinase inhibitor, Vascular Growth Factor Receptor [VGFR] kinase inhibitor, Fibroblast Growth Factor Receptor [FGFR] kinase inhibitor, Platelet-derived Growth Factor Receptor [PGFR] I kinase inhibitor, and Bcr-Abl kinase inhibitors such as STI-571, Gleevec, and Glivec]); antisense molecules; antibodies [e.g., Herceptin and Rituxan]; anti-estrogens [e.g., raloxifene and tamoxifen]; anti-androgens [e.g., flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids]; cyclooxygenase 2 (COX-2) inhibitors [e.g., Celecoxib, meloxicam, NS-398, and non-steroidal antiinflammatory drugs (NSAIDs)]; and cancer chemotherapeutic drugs [e.g., irinotecan (Camptosar), CPT-11, fludarabine (Fludara), dacarbazine (DTIC), dexamethasone, mitoxantrone, Mylotarg, VP-16, cisplatinum, 5-FU, Doxrubicin, Taxotere or taxol]; cellular signaling molecules; ceramides and cytokines; and staurosprine, and the like.

In other aspects, the present invention provides pharmaceutical compositions comprising at least one compound of formula I, II, III, IV or V together with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

In other aspects, the present invention provides methods of manufacture of compounds of formula I, II, III, IV or V as described herein.

In yet other aspects, the present invention provides compounds which are inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of $p21^{ras}$, the instant inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal, e.g., murine cancer, since the

progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore is susceptible to treatment by interruption of the cascade by inhibiting raf kinase activity. Accordingly, the compounds of the invention are useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon, myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

"Raf inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to Raf Kinase activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the Raf/Mek Filtration Assay described generally hereinbelow. Preferred isoforms of Raf Kinase in which the compounds of the present invention will be shown to inhibit, include A-Raf, B-Raf, and C-Raf (Raf-1). "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme (e.g., Raf kinase) to half-maximal level. Representative compounds of the present invention have been discovered to exhibit inhibitory activity against Raf. Compounds of the present invention preferably exhibit an IC_{50} with respect to Raf of no more than about 10 μM, more preferably, no more than about 5 μM, even more preferably not more than about 1 μM, and most preferably, not more than about 200 nM, as measured in the Raf kinase assays described herein.

As used herein, the term "benz-azoles" includes benzimidazoles, benzothiazoles and benzoxazoles.

The phrase "alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. The phrase also includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus the phrase alkyl groups

includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 12 carbon atoms.

As used herein "loweralkyl" includes both substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 6 carbon atoms. Representative loweralkyl groups include, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl, tert-butyl, neopentyl, trifluoromethyl, pentafluoroethyl and the like. Loweralkyl groups may be substituted, such as with halo, hydroxy, amino, nitro and/or cyano groups, and the like. Representative of halo-substituted and hydroxy-substituted loweralkyl include chloromethyl, trichloromethyl, chloroethyl, hydroxyethyl, and the like. Other suitable substituted loweralkyl moieties include, for example, aralkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonyl-aminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

"Loweralkoxy" as used herein refers to RO- wherein R is loweralkyl. Representative examples of loweralkoxy groups include methoxy, ethoxy, *t*-butoxy, trifluoromethoxy and the like.

As used herein, the term "halogen" or "halo" refers to chloro, bromo, fluoro and iodo groups. "Haloalkyl" refers to an alkyl radical substituted with one or more halogen atoms. The term "haloloweralkyl" refers to a loweralkyl radical substituted with one or more halogen atoms. The term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. The term "haloloweralkoxy" refers to a loweralkoxy radical substituted with one or more halogen atoms.

"Amino" refers herein to the group $-NH_2$. The term "alkylamino" refers herein to the group –NRR' where R and R' are each independently selected from hydrogen or a lower alkyl. The term "arylamino" refers herein to the group –NRR' where R is aryl and R' is hydrogen, a lower alkyl, or an aryl. The term "aralkylamino" refers herein to the group –NRR' where R is a lower aralkyl and R' is hydrogen, a loweralkyl, an aryl, or a lowearalkyl.

The term "alkoxyalkyl" refers to the group $-alk_1-O-alk_2$ where alk_1 is alkyl or alkenyl, and alk_2 is alkyl or alkenyl. The term "loweralkoxyalkyl" refers to an alkoxyalkyl where alk_1 is loweralkyl or loweralkenyl, and alk_2 is loweralkyl or loweralkenyl. The term "aryloxyalkyl" refers to the group –alkyl-O-aryl. The term "aralkoxyalkyl" refers to the group -alkylenyl-O-aralkyl, where aralkyl is a lowearalkyl.

The term "alkoxyalkylamino" refers herein to the group –NR-(alkoxyalkyl), where R is typically hydrogen, loweraralkyl, or loweralkyl. The term "aminoloweralkoxyalkyl" refers herein to an aminoalkoxyalkyl in which the alkoxyalkyl is a loweralkoxyalkyl.

The term "aminocarbonyl" refers herein to the group $-C(O)-NH_2$. "Substituted aminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweralkyl and R' is hydrogen or a loweralkyl. The term "arylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is an aryl and R' is hydrogen, loweralkyl or aryl. "aralkylaminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweraralkyl and R' is hydrogen, loweralkyl, aryl, or loweraralkyl.

"Aminosulfonyl" refers herein to the group $-S(O)_2-NH_2$. "Substituted aminosulfonyl" refers herein to the group $-S(O)_2-NRR'$ where R is loweralkyl and R' is hydrogen or a loweralkyl. The term "aralkylaminosulfonlyaryl" refers herein to the group –aryl-$S(O)_2$–NH-aralkyl, where the aralkyl is loweraralkyl.

"Carbonyl" refers to the divalent group –C(O)-.

"Carbonyloxy" refers generally to the group –C(O)-O. Such groups include esters, -C(O)-O-R, where R is loweralkyl, cycloalkyl, aryl, or loweraralkyl. The term "carbonyloxycycloalkyl" refers generally herein to both an "carbonyloxycarbocycloalkyl" and an "carbonyloxyheterocycloalkyl", i.e., where R is a carbocycloalkyl or heterocycloalkyl, respectively. The term "arylcarbonyloxy" refers herein to the group –C(O)-O-aryl, where aryl is a mono- or polycyclic, carbocycloaryl or heterocycloaryl. The term "aralkylcarbonyloxy" refers herein to the group –C(O)-O-aralkyl, where the aralkyl is loweraralkyl.

The term "sulfonyl" refers herein to the group $-SO_2-$. "Alkylsulfonyl" refers to a substituted sulfonyl of the structure $-SO_2R-$ in which R is alkyl. Alkylsulfonyl groups employed in compounds of the present invention are typically loweralkylsulfonyl groups having from 1 to 6 carbon atoms in its backbone structure. Thus, typical alkylsulfonyl groups employed in compounds of the present invention include, for example, methylsulfonyl (i.e., where R is methyl), ethylsulfonyl (i.e., where R is ethyl), propylsulfonyl (i.e., where R is propyl), and the like. The term "arylsulfonyl" refers herein to the group $-SO_2-$aryl. The term "aralkylsulfonyl" refers herein to the group $-SO_2-$aralkyl, in which the aralkyl is loweraralkyl. The term "sulfonamido" refers herein to $-SO_2NH_2$.

As used herein, the term "carbonylamino" refers to the divalent group -NH-C(O)- in which the hydrogen atom of the amide nitrogen of the carbonylamino group can be replaced a loweralkyl, aryl, or lowearalkyl group. Such groups include moieties such as carbamate esters (-NH-C(O)-O-R) and amides –NH-C(O)-O-R, where R is a straight or branched chain loweralkyl, cycloalkyl, or aryl or lowearalkyl. The term "loweralkylcarbonylamino" refers to alkylcarbonylamino where R is a loweralkyl having from 1 to about 6 carbon atoms in its backbone structure. The term "arylcarbonylamino" refers to group –NH-C(O)-R where R is an aryl. Similarly, the term "aralkylcarbonylamino " refers to carbonylamino where R is a lower aralkyl. As used herein, the term "aminocarbonyl" refers to the divalent group -C(O)-NH- in which the hydrogen atom of the amide nitrogen of the carbonylamino group can be replaced a loweralkyl, aryl, or lowearalkyl group, as described above.

As used herein, the term "guanidino" or "guanidyl" refers to moieties derived from guanidine, H_2N-C(=NH)-NH_2. Such moieties include those bonded at the nitrogen atom carrying the formal double bond (the "2"-position of the guanidine, e.g., diaminomethyleneamino, $(H_2N)_2C$=NH-) and those bonded at either of the nitrogen atoms carrying a formal single bond (the "1-" and/or "3"-positions of the guandine, e.g., H_2N-C(=NH)-NH-). The hydrogen atoms at any of the nitrogens can be replaced with a suitable substituent, such as loweralkyl, aryl, or lowearalkyl.

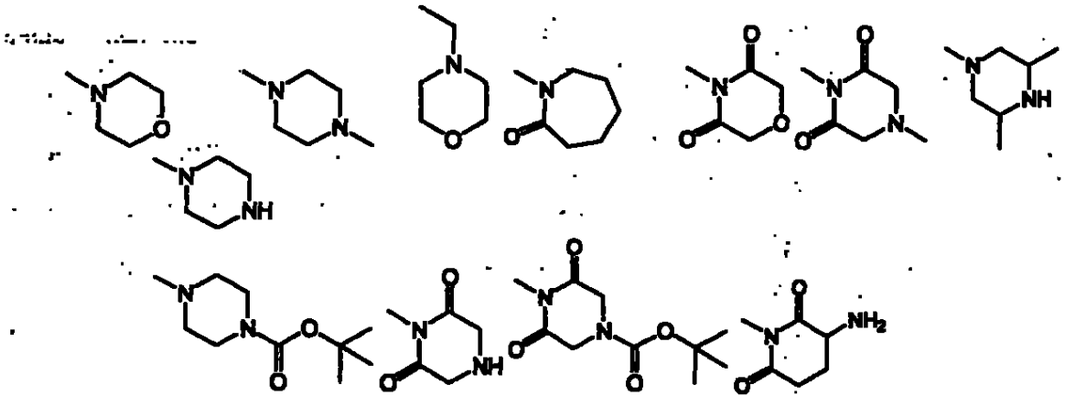
As used herein, the term "amidino" refers to the moieties R-C(=N)-NR′- (the radical being at the "N^1" nitrogen) and R(NR′)C=N- (the radical being at the "N^2" nitrogen), where R and R′ can be hydrogen, loweralkyl, aryl, or lowearalkyl.

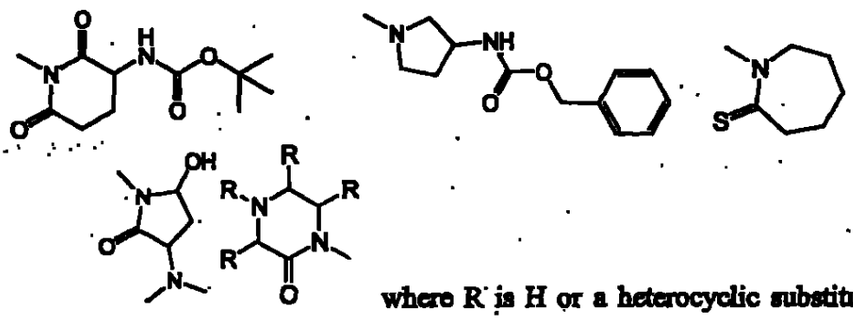
"Cycloalkyl" refers to a mono- or polycyclic, heterocyclic or carbocyclic alkyl substituent. Typical cycloalkyl substituents have from 3 to 8 backbone (i.e., ring) atoms in which each backbone atom is either carbon or a heteroatom. The term "heterocycloalkyl" refers herein to cycloalkyl substituents that have from 1 to 5, and more typically from 1 to 4 heteroatoms in the ring structure. Suitable heteroatoms employed in compounds of the present invention are nitrogen, oxygen, and sulfur. Representative heterocycloalkyl moieties include, for example, morpholino, piperazinyl, piperadinyl and the like. Carbocycloalkyl groups are cycloalkyl groups in which all ring atoms are carbon. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures.

The term "substituted heterocycle" or "heterocyclic group" or heterocycle as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from nitrogen, oxygen, and sulfur or a 5- or 6-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur; wherein the 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur atom maybe optionally oxidized; wherein the nitrogen and sulfur heteroatoms maybe optionally quarternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5- or 6-membered heterocyclic ring independently defined above. The term "heterocycle" thus includes rings in which nitrogen is the heteroatom as well as partially and fully-saturated rings. Preferred heterocycles include, for example: diazapinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazoyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, N-methylazetidinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl and benzothienyl.

Heterocyclic moieties can be unsubstituted or monosubstituted or disubstituted with various substituents independently selected from hydroxy, halo, oxo (C=O), alkylimino (RN=, wherein R is a loweralkyl or loweralkoxy group), amino, alkylamino, dialkylamino, acylaminoalkyl, alkoxy, thioalkoxy, polyalkoxy, loweralkyl, cycloalkyl or haloalkyl.

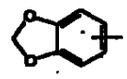
The heterocyclic groups may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.





where R is H or a heterocyclic substituent, as described herein.

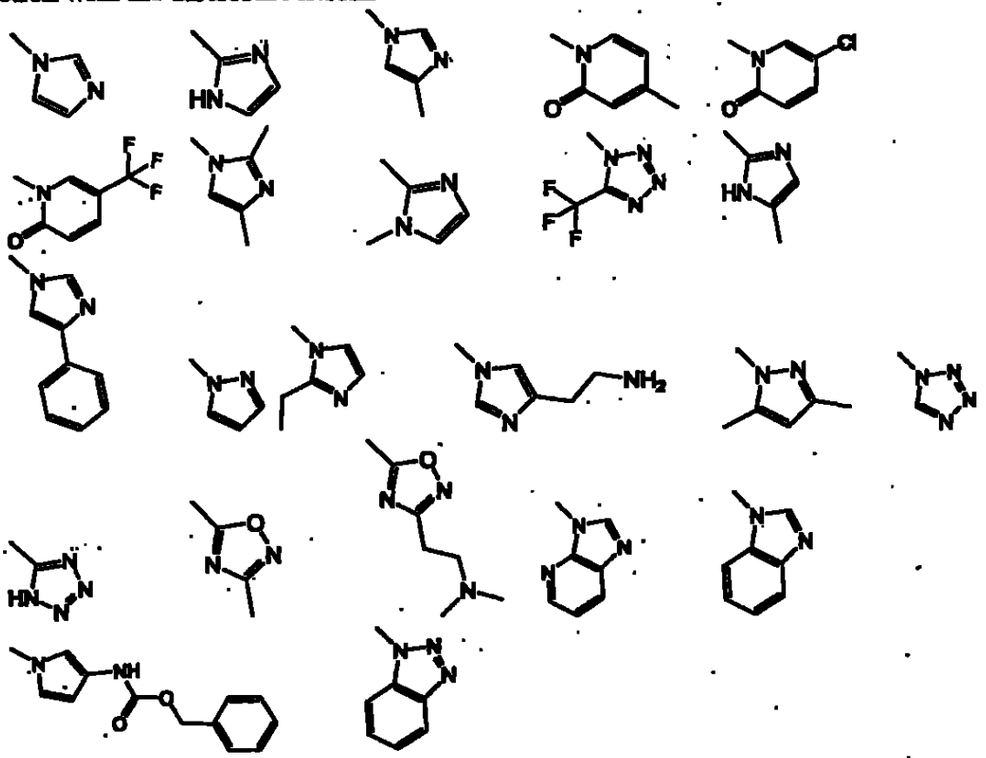
Representative heterocyclics include, for example, imidazolyl, pyridyl, piperazinyl, azetidinyl, thiazolyl, furanyl, triazolyl benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, indolyl, naphthpyridinyl, indazolyl, and quinolizinyl.

"Aryl" refers to optionally substituted monocyclic and polycyclic aromatic groups having from 3 to 14 backbone carbon or hetero atoms, and includes both carbocyclic aryl groups and heterocyclic aryl groups. Carbocyclic aryl groups are aryl groups in which all ring atoms in the aromatic ring are carbon. The term "heteroaryl" refers herein to aryl groups having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms. When used in connection with aryl substituents, the term "polycyclic aryl" refers herein to fused and non-fused cyclic structures in which at least one cyclic structure is aromatic, such as, for example, benzodioxozolo (which has a heterocyclic structure fused to a phenyl group, i.e.,  , naphthyl, and the like. Exemplary aryl moieties employed as substituents in compounds of the present invention include phenyl, pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl, and the like.

"Aralkyl" refers to an alkyl group substituted with an aryl group. Typically, aralkyl groups employed in compounds of the present invention have from 1 to 6 carbon atoms incorporated within the alkyl portion of the aralkyl group. Suitable aralkyl groups employed in compounds of the present invention include, for example, benzyl, picolyl, and the like.

Representative heteroaryl groups include, for example, those shown below. These heteroaryl groups can be further substituted and may be attached at various positions as

will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



Representative heteroaryl's include, for example, imidazolyl, pyridyl, piperazinyl, azetidinyl, thiazolyl, triazolyl benzimidazolyl, benzothiazolyl, and benzoxazolyl.

The term "biaryl" refers to a group or substituent to which two aryl groups, which are not condensed to each other, are bound. Exemplary biaryl compounds include, for example, phenylbenzene, diphenyldiazene, 4-methylthio-1-phenylbenzene, phenoxybenzene, (2-phenylethynyl)benzene, diphenyl ketone, (4-phenylbuta-1,3-diynyl)benzene, phenylbenzylamine, (phenylmethoxy)benzene, and the like. Preferred optionally substituted biaryl groups include: 2-(phenylamino)-N-[4-(2-phenylethynyl)-phenyl]acetamide, 1,4-diphenylbenzene, N-[4-(2-phenylethynyl)phenyl]-2-[benzyl-amino]acetamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]propanamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(cyclopropylamino)-N-[4-(2-phenylethynyl)-phenyl]acetamide, 2-(ethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-[(2-methylpropyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 5-phenyl-2H-benzo-

[d]1,3-dioxolene, 2-chloro-1-methoxy-4-phenylbenzene, 2-[(imidazolylmethyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-phenoxybenzene, N-(2-aminoethyl)-[4-(2-phenylethynyl)phenyl]carboxamide, 2-{[(4-fluorophenyl)methyl]amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-{[(4-methylphenyl)methyl]amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-(trifluoromethyl)benzene, 1-butyl-4-phenylbenzene, 2-(cyclohexylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethylmethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(butylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(4-pyridylamino)acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(quinuclidin-3-ylamino)acetamide, N-[4-(2-phenylethynyl)phenyl]pyrrolidin-2-ylcarboxamide, 2-amino-3-methyl-N-[4-(2-phenylethynyl)-phenyl]butanamide, 4-(4-phenylbuta-1,3-diynyl)phenylamine, 2-(dimethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 2-(ethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 4-ethyl-1-phenylbenzene, 1-[4-(2-phenylethynyl)phenyl]ethan-1-one, N-(1-carbamoyl-2-hydroxypropyl)[4-(4-phenylbuta-1,3-diynyl)phenyl]carboxamide, N-[4-(2-phenylethynyl)phenyl]propanamide, 4-methoxyphenyl phenyl ketone, phenyl-N-benzamide, (tert-butoxy)-N-[(4-phenylphenyl)methyl]carboxamide, 2-(3-phenylphenoxy)ethanehydroxamic acid, 3-phenylphenyl propanoate, 1-(4-ethoxyphenyl)-4-methoxybenzene, and [4-(2-phenylethynyl)phenyl]pyrrole.

The term "heteroarylaryl" refers to a biaryl group where one of the aryl groups is a heteroaryl group. Exemplary heteroarylaryl groups include, for example, 2-phenylpyridine, phenylpyrrole, 3-(2-phenylethynyl)pyridine, phenylpyrazole, 5-(2-phenylethynyl)-1,3-dihydropyrimidine-2,4-dione, 4-phenyl-1,2,3-thiadiazole, 2-(2-phenylethynyl)pyrazine, 2-phenylthiophene, phenylimidazole, 3-(2-piperazinylphenyl)-furan, 3-(2,4-dichlorophenyl)-4-methylpyrrole, and the like. Preferred optionally substituted heteroarylaryl groups include: 5-(2-phenylethynyl)pyrimidine-2-ylamine, 1-methoxy-4-(2-thienyl)benzene, 1-methoxy-3-(2-thienyl)benzene, 5-methyl-2-phenylpyridine, 5-methyl-3-phenylisoxazole, 2-[3-(trifluoromethyl)phenyl]furan, 3-fluoro-5-(2-furyl)-2-methoxy-1-prop-2-enylbenzene, (hydroxyimino)(5-phenyl(2-thienyl))-

methane, 5-[(4-methylpiperazinyl)methyl]-2-phenylthiophene, 2-(4-ethylphenyl)thiophene, 4-methylthio-1-(2-thienyl)benzene, 2-(3-nitrophenyl)thiophene, (tert-butoxy)-N-[(5-phenyl(3-pyridyl))methyl]carboxamide, hydroxy-N-[(5-phenyl(3-pyridyl))methyl]-amide, 2-(phenylmethylthio)pyridine, and benzylimidazole.

The term "heteroarylheteroaryl" refers to a biaryl group where both of the aryl groups is a heteroaryl group. Exemplary heteroarylheteroaryl groups include, for example, 3-pyridylimidazole, 2-imidazolylpyrazine, and the like. Preferred optionally substituted heteroarylheteroaryl groups include: 2-(4-piperazinyl-3-pyridyl)furan, diethyl-(3-pyrazin-2-yl(4-pyridyl))amine, and dimethyl{2-[2-(5-methylpyrazin-2-yl)ethynyl](4-pyridyl)}amine.

"Optionally substituted" or "substituted" refers to the replacement of hydrogen with a monovalent or divalent radical. Suitable substitution groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, halologweralkyl, loweralkyamino, halologweralkylamino, loweralkoxy, halologweralkoxy, loweralkoxyalkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like.

The substitution group can itself be substituted. The group substituted onto the substitution group can be carboxyl, halo; nitro, amino, cyano, hydroxyl, loweralkyl, loweralkoxy, aminocarbonyl, -SR, thioamido, $-SO_3H$, $-SO_2R$ or cycloalkyl, where R is typically hydrogen, hydroxyl or loweralkyl.

When the substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substitutents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms.

As used herein, the term "carboxy-protecting group" refers to a carbonyl group which has been esterified with one of the commonly used carboxylic acid protecting ester groups employed to block or protect the carboxylic acid function while reactions involving other functional sites of the compound are carried out. In addition, a carboxy

protecting group can be attached to a solid support whereby the compound remains connected to the solid support as the carboxylate until cleaved by hydrolytic methods to release the corresponding free acid. Representative carboxy-protecting groups include, for example, loweralkyl esters, secondary amides and the like.

As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds of Formula I. These salts can be prepared *in situ* during the final isolation and purification of the compounds of Formula I, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not

limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters, which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

The term "cancer" refers to cancer diseases that can be beneficially treated by the inhibition of Raf kinase, including, for example, solid cancers, such as carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) and adenomas (e.g., villous colon adenoma).

In illustrative embodiments of the invention, Ar_1 may be, for example, phenyl which may be substituted by one or more substitutents selected from the group consisting of hydroxyl, nitro, cyano, halo, and substituted or unsubstituted amino, imino, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, halologeralkyl, loweralkyamino, halologeralkylamino, loweralkoxy, halologeralkoxy, loweralkoxyalkyl, alkylcarbonyl,

aminocarbonyl, loweralkylaminocarbonyl, heterocycloalkylloweralkylaminocarbonyl, carboxylloweralkylaminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like. In other illustrative embodiments of the invention, Ar_2 may be, for example, pyridyl, which may be substituted by one or more substitutents selected from the group consisting of hydroxyl, nitro, cyano, halo, and substituted or unsubstituted amino, imino, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkyamino, haloloweralkylamino, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, alkylcarbonyl, aminocarbonyl, loweralkylaminocarbonyl, heterocycloalkylloweralkylaminocarbonyl, carboxylloweralkylaminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like.

In representative embodiments of the invention, the compounds of the invention include, for example, 4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, 4-({2-[(3-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(3-chloro-4-fluorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, N-methyl-4-{[2-(phenylamino)-1H-benzimidazol-6-yl]oxy}pyridine-2-carboxamide, 4-[(2-{[4-bromo-2-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(2-methylpropyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, 4-[(2-{[4-(dimethylamino)naphthalen-1-yl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(4-nitrophenyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, N-methyl-4-({2-[(phenylcarbonyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, N-methyl-4-({2-[(phenylmethyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, methyl 4-{[6-({2-[(methylamino)carbonyl]pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}benzoate, 4-({2-[(4-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-[(2-{[2-(ethyloxy)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(2-morpholin-4-ylethyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, 4-({2-[(4-iodophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, N-methyl-4-[(2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]pyridine-2-carboxamide,

4-({2-[(furan-2-ylmethyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(4-bromo-3-methylphenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(4-acetylphenyl)amino]-1H-benzimidazol-6-yl}-oxy)-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(2,4,6-trimethylphenyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, 4-[(2-{[4-(1,1-dimethylethyl)-phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, 4-({2-[(2-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(3-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(2-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, methyl 3-{[6-({2-[(methylamino)carbonyl]pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}thiophene-2-carboxylate, 4-({2-[(4-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-{(3R,5R)-5-[(methyloxy)methyl]pyrrolidin-3-yl}pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide, 4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-ethylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2,2,2-trifluoroethyl)pyridine-2-carboxamide, N-(4-bromophenyl)-1-methyl-5-{[2-(pyrrolidin-1-ylcarbonyl)pyridin-4-yl]oxy}-1H-benzimidazol-2-amine, ethyl (3R)-3-(methyloxy)-4-[({4-[(2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-carbonyl)amino]piperidine-1-carboxylate, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(dimethylamino)ethyl]pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(tetrahydrofuran-2-yl-methyl)pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(piperidin-4-ylmethyl)pyridine-2-carboxamide, 5-({2-[(3-aminopyrrolidin-1-yl)carbonyl]pyridin-4-yl}oxy)-N-(4-bromophenyl)-1-methyl-1H-benzimidazol-2-amine, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[1-(diphenylmethyl)azetidin-3-yl]pyridine-2-

carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-piperidin-3-ylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(1,3-thiazol-2-yl)pyridine-2-carboxamide, and 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[(1-ethylpyrrolidin-2-yl)-methyl]pyridine-2-carboxamide, (4-{2-[(4-bromophenyl)amino]benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide, (4-{2-[(4-bromophenyl)amino]benzoxazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide, and other representative compounds set forth in the Examples.

In other aspects, the present invention relates to the processes for preparing the compounds of Formulas I, II, III, IV and V and to the synthetic intermediates useful in such processes.

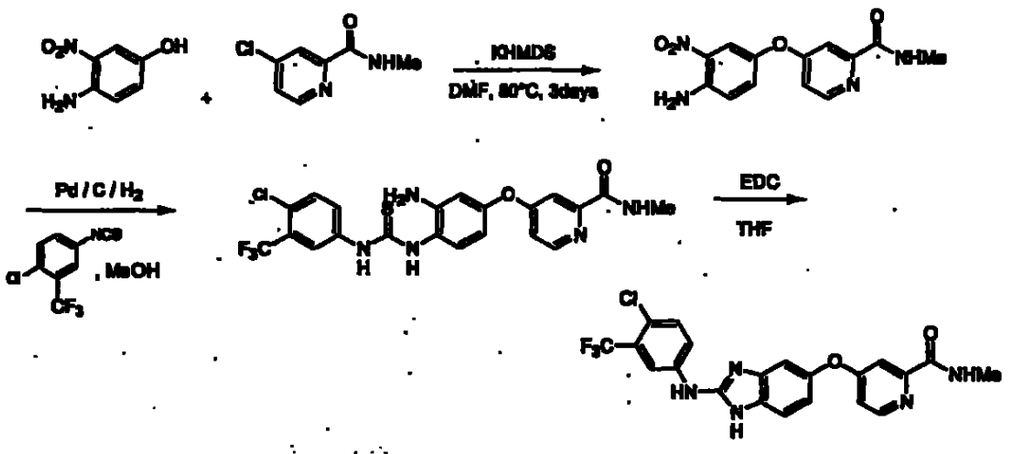
The compounds of the invention comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of the invention comprising mixtures of stereoisomers at a particular asymmetrically substituted carbon atom or a single stereoisomer. As a result, racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY, *Pure Appl. Chem.* 45:13-30 (1976). The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the CHEMICAL ABSTRACTS INDEX GUIDE-APPENDIX IV (1987) paragraph 203.

The present invention also relates to the processes for preparing the compounds of the invention and to the synthetic intermediates useful in such processes, as described in detail below.

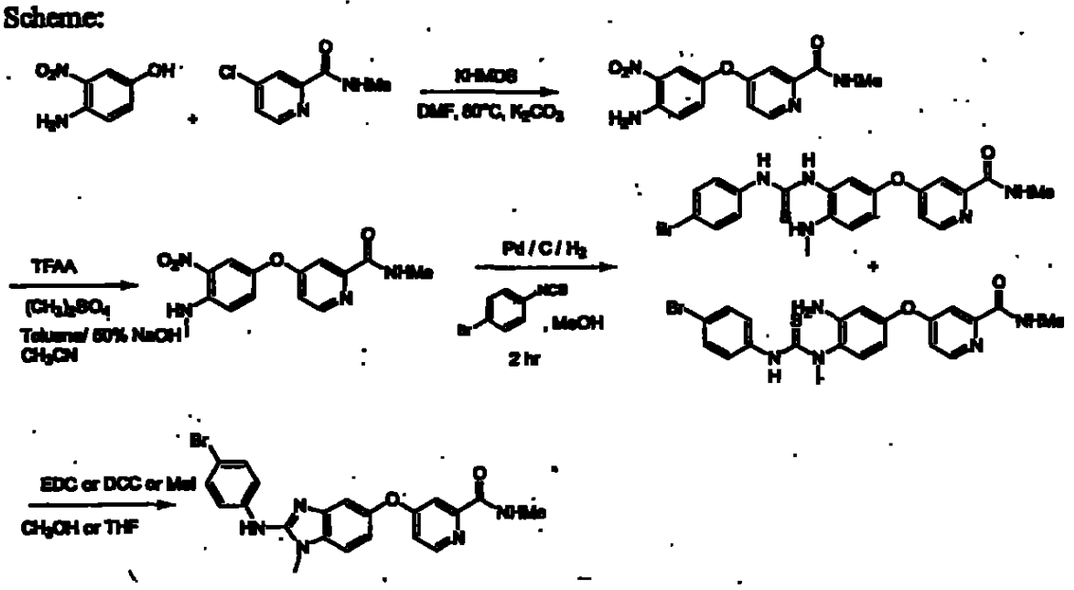
Synthetic Methods

Compounds of the invention containing a benzimidazole core may be prepared using a number of methods familiar to one of skill in the art. In one method, suitably functionalized diamines may be coupled with various thioisocyanates to form the

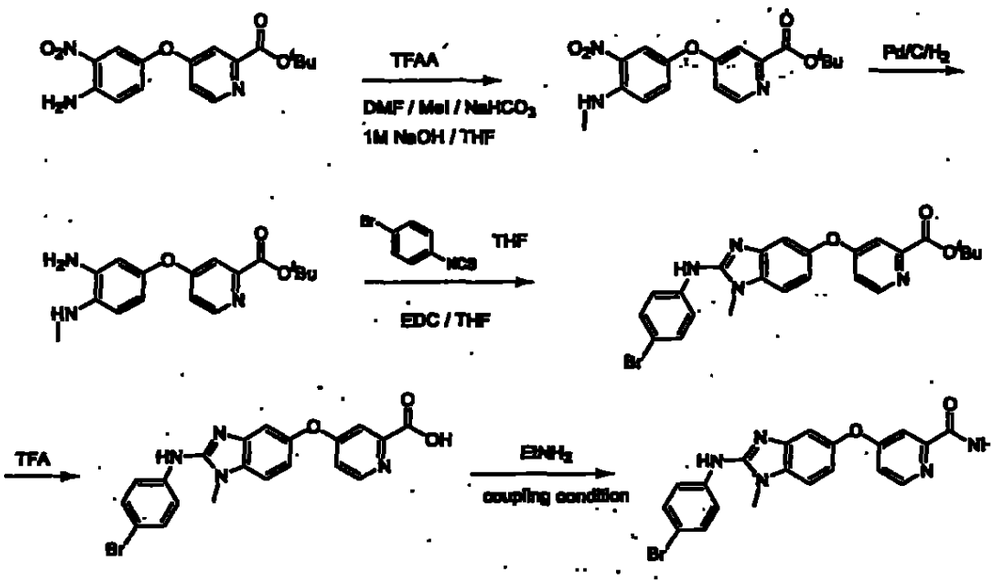
intermediate thioureas. Cyclization to form the benzimidazole moiety may be effected under known conditions such as with treatment carbodiimides or alkyl halides as in the following schemes.



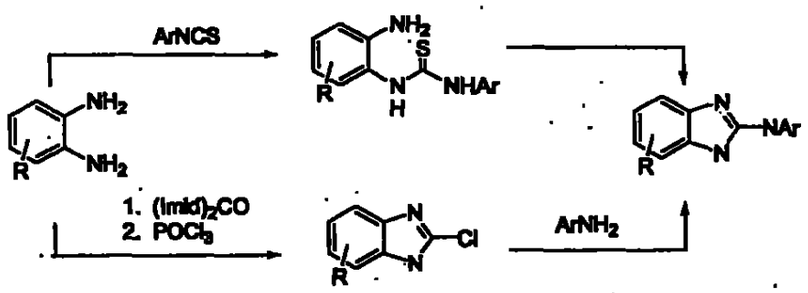
Scheme:



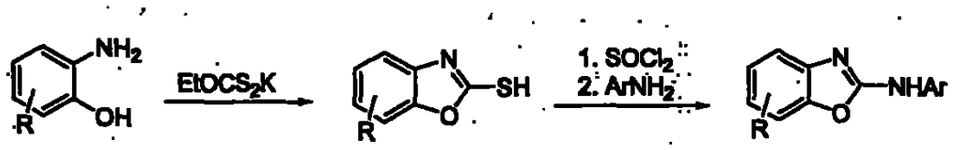
Scheme:



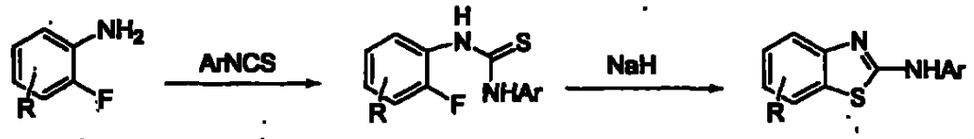
Alternatively the diamines may be reacted sequentially with carbonyl diimidazole and phosphoryl chloride followed by coupling with the appropriate amine.



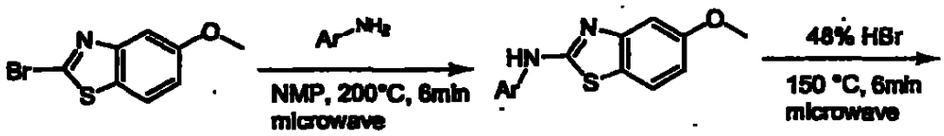
Compounds containing the oxazole structure may similarly be prepared according to the methods above or according to other known general procedures. Haviv et al. (*J. Med. Chem.* 1988, 31:1719) describes a procedure for assembling oxazole cores wherein a hydroxy aniline is treated with ethyl potassium xanthate. The resulting sulfuryl benzoxazole may then be chlorinated and coupled with an amine.

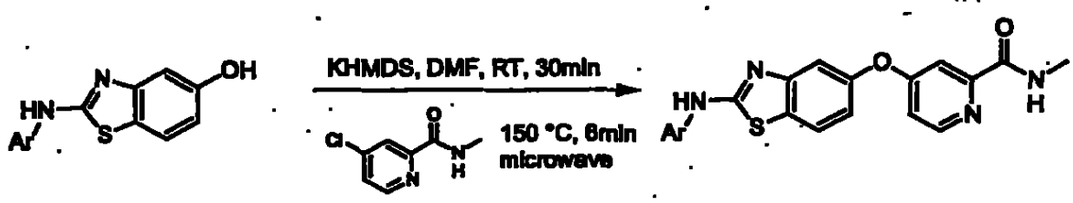


Compounds containing a benzothiazole core may also be prepared according to known methods. An ortho-halothioisocyanate may be reacted with an amine to form a thiourea. Reduction with NaH then allows formation of the thiazole ring.

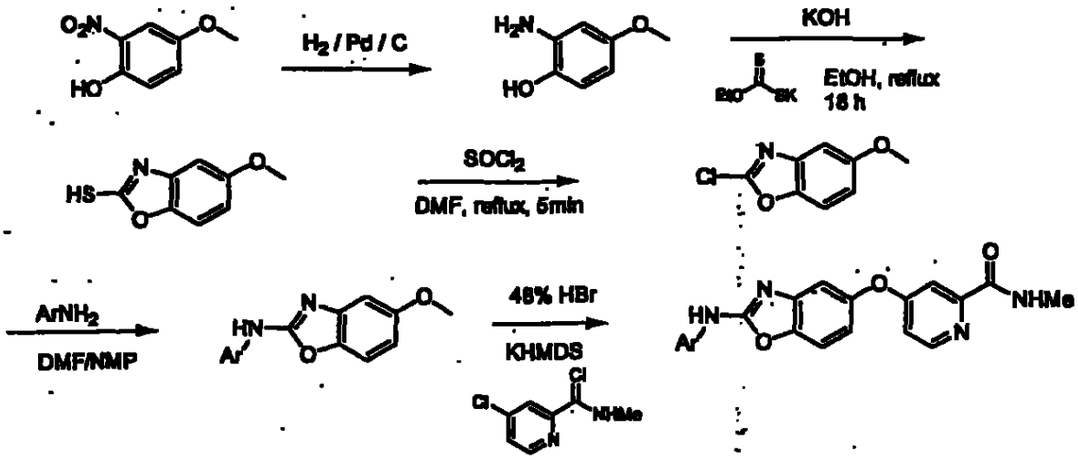


Benzothiazoles may generally be substituted in accordance with the present invention, such as through the following synthetic pathway:





Benzoxzoles may generally be synthesized through the following pathway:



The compounds of the invention are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient. Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinyl-pyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991), incorporated herein by reference.

Effective amounts of the compounds of the invention generally include any amount sufficient to detectably inhibit Raf activity by any of the assays described herein, by other Raf kinase activity assays known to those having ordinary skill in the art or by detecting an inhibition or alleviation of symptoms of cancer.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

For purposes of the present invention, a therapeutically effective dose will generally be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The compounds of the present invention may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of

transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically

acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 *et seq.* (1976).

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents used in the treatment of cancer. Representative agents useful in combination with the compounds of the invention for the treatment of cancer include, for example, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, trastuzumab, as well as other cancer chemotherapeutic agents.

The above compounds to be employed in combination with the compounds of the invention will be used in therapeutic amounts as indicated in the *Physicians' Desk Reference* (PDR) 47th Edition (1993), which is incorporated herein by reference, or such therapeutically useful amounts as would be known to one of ordinary skill in the art.

The compounds of the invention and the other anticancer agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions, which are given at the same time or different times, or the therapeutic agents, can be given as a single composition.

Antiestrogens, such as tamoxifen, inhibit breast cancer growth through induction of cell cycle arrest, that requires the action of the cell cycle inhibitor p27Kip. Recently, it has been shown that activation of the Ras-Raf-MAP Kinase pathway alters the phosphorylation status of p27Kip such that its inhibitory activity in arresting the cell cycle is attenuated, thereby contributing to antiestrogen resistance (Donovan et al, *J. Biol. Chem. 276*:40888, 2001). As reported by Donovan et al., inhibition of MAPK signaling

through treatment with MEK inhibitor changed the phosphorylation status of p27 in hormone refactory breast cancer cell lines and in so doing restored hormone sensitivity. Accordingly, in one aspect, the compounds of formulas (I), (II), (III), (IV) and (V) may be used in the treatment of hormone dependent cancers, such as breast and prostate cancers, to reverse hormone resistance commonly seen in these cancers with conventional anticancer agents.

In hematological cancers, such as chronic myelogenous leukemia (CML), chromosomal translocation is responsible for the constitutively activated BCR-AB1 tyrosine kinase. The afflicted patients are responsive to Geevec, a small molecule tyrosine kinase inhibitor, as a result of inhibition of Ab1 kinase activity. However, many patients with advanced stage disease respond to Gleevec initially, but then relapse later due to resistance-conferring mutations in the Ab1 kinase domain. *In vitro* studies have demonstrated that BCR-Av1 employs the Raf kinase pathway to elicit its effects. In addition, inhibiting more than one kinase in the same pathway provides additional protection against resistance-conferring mutations. Accordingly, in another aspect of the invention, the compounds of formulas (I), (II), (III), (IV) and (V) are used in combination with at least one additional agent, such as Gleevec, in the treatment of hematological cancers, such as chronic myelogenous leukemia (CML), to reverse or prevent resistance to the at least one additional agent.

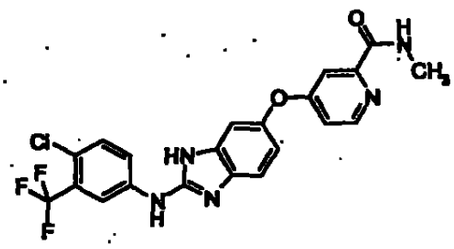
The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

Representative side chains for use in the compounds of the following examples may generally be prepared in accordance with the following procedures:

Example 1

Synthesis of 4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide

The compound 4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide was synthesized as follows:



Step 1. Synthesis of 4-[(4-amino-3-nitrophenyl)oxy]-*N*-methylpyridine-2-carboxamide:

A mixture containing 4-amino-3-nitrophenol (1eq) and potassium bis(trimethylsilyl)amide (2eq) was stirred in dimethylformamide for 2 hours at room temperature. To this mixture was added (4-chloro(2-pyridyl))-*N*-methylcarboxamide (1eq) and potassium carbonate (1.2eq) and stirred at 90°C for 3 days. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried, filtered, and concentrated in vacuum to give brown solid. Purification on silica gel (2% triethyl amine / 50% ethyl acetate in hexane) gave 4-[(4-amino-3-nitrophenyl)oxy]-*N*-methylpyridine-2-carboxamide as an orange solid. The product gave satisfactory NMR. HPLC, 3.39 min; MS: MH+ = 289.

Step 2. Synthesis of 4-[(3,4-diaminophenyl)oxy]-N-methylpyridine-2-carboxamide:

The mixture containing [4-(3-amino-4-nitrophenoxy)(2-pyridyl)]-N- in methanol with catalytic amount of 10%Pd/C was hydrogenated until disappearance of the yellow color to yield the product amine. HPLC, 2.5 mins; MS: MH+ = 259.

Step 3. Synthesis of 4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide:

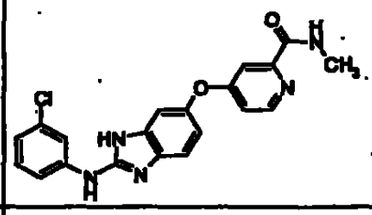
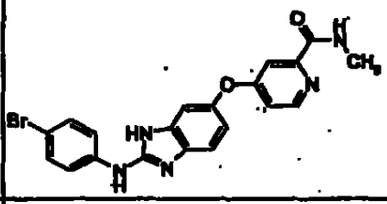
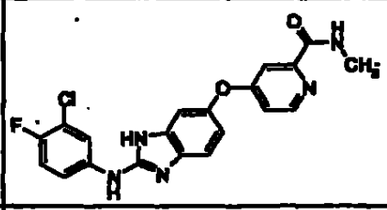
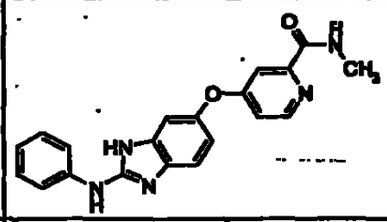
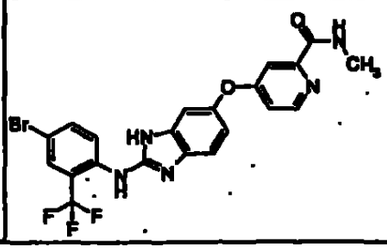
The mixture containing 4-[(3,4-diaminophenyl)oxy]-N-methylpyridine-2-carboxamide (1eq) and 4-chloro-3-(trifluoromethyl)benzeneisothiocyanate (1eq) in tetrahydrofuran was stirred at room temperature for 16 hours to give the corresponding thiourea. To the resulting mixture was added 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (2eq) and the mixture was stirred for another 10 hours. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried. Purification on HPLC gave 4-[(2-

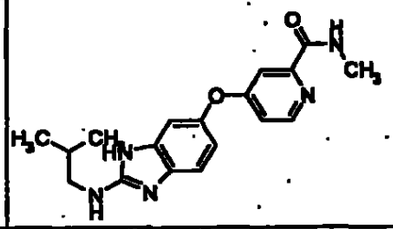
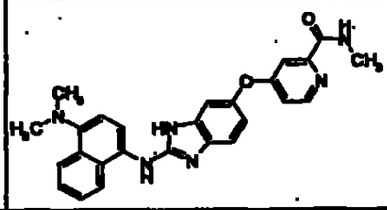
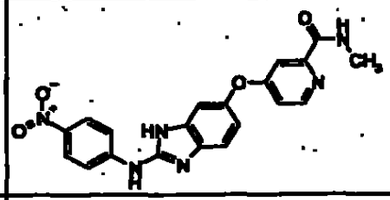
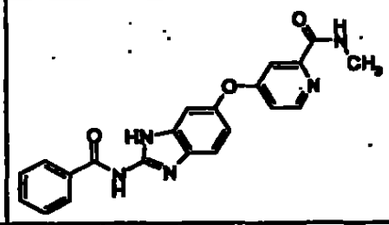
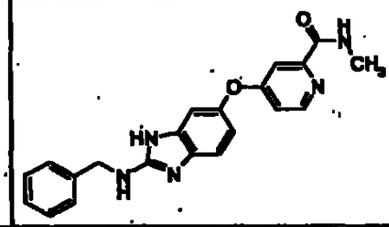
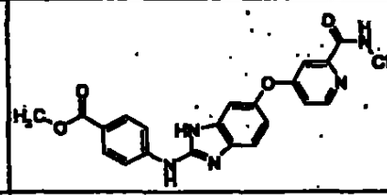
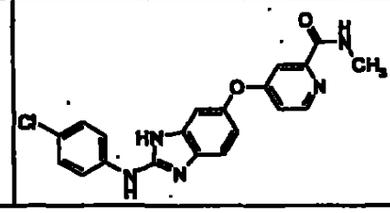
{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methyl-pyridine-2-carboxamide. MS: MH+ = 462

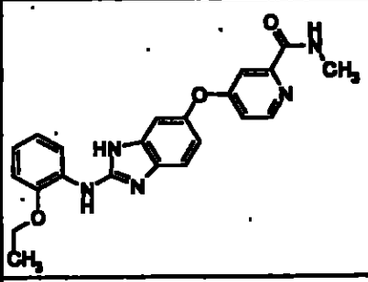
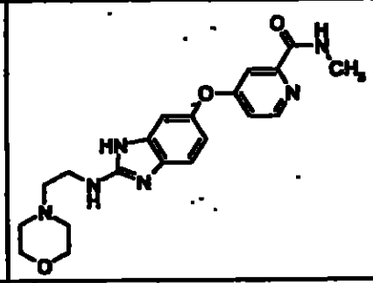
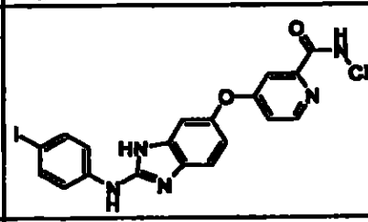
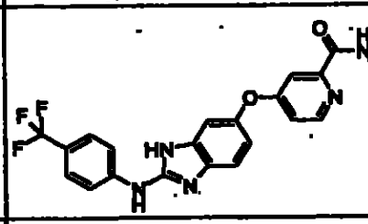
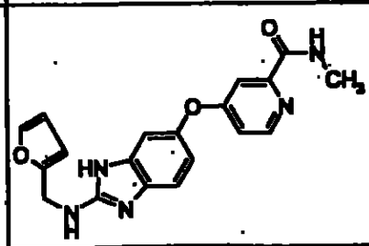
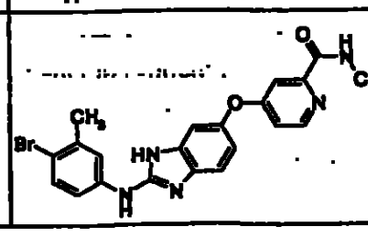
Examples 2-108

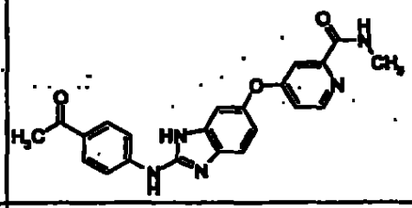
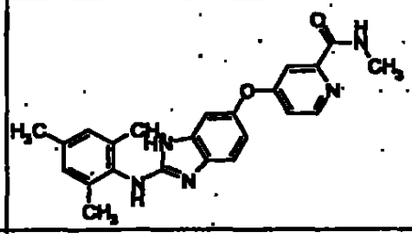
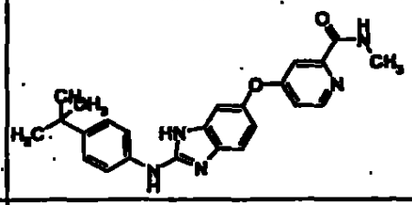
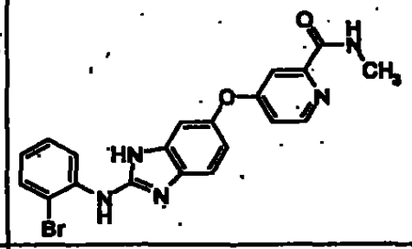
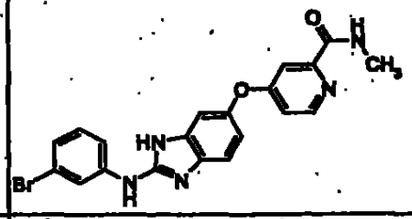
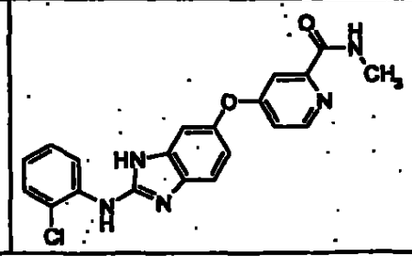
The compounds shown in the following Table 1 (Examples 2-108) were prepared from following the procedure described for Example 1.

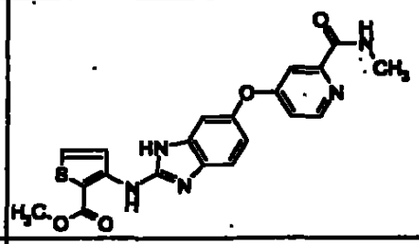
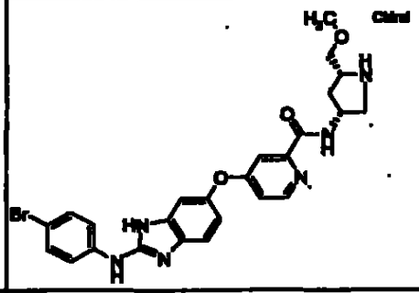
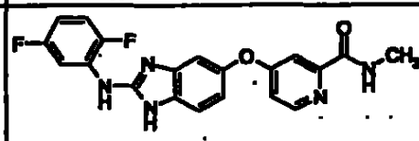
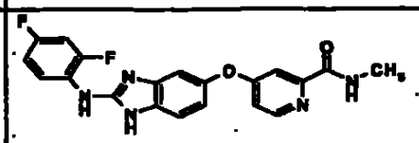
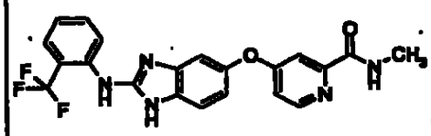
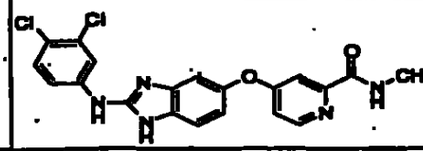
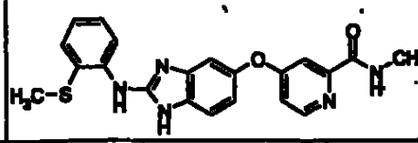
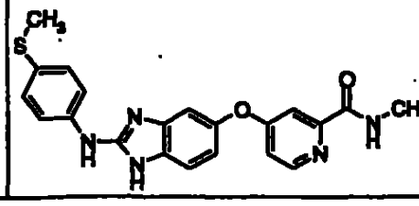
Table 1

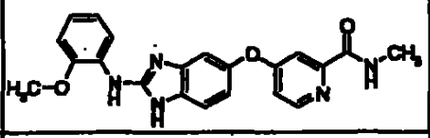
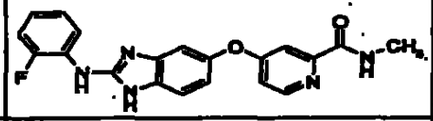
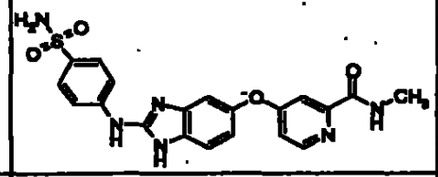
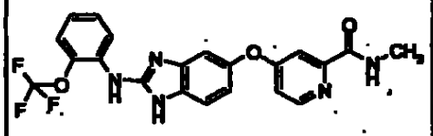
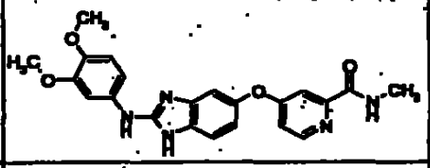
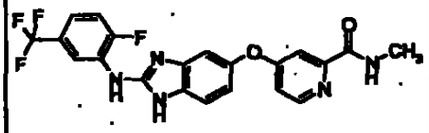
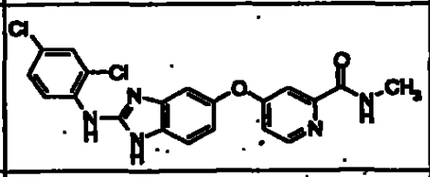
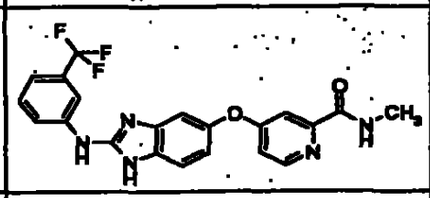
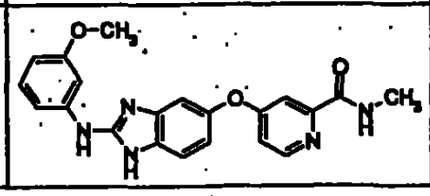
Example	Structure	Name	MH+
2		4-({2-[(3-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methyl-pyridine-2-carboxamide	394
3		4-({2-[(4-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide	440
4		4-({2-[(3-chloro-4-fluorophenyl)-amino]-1H-benzimidazol-6-yl}-oxy)-N-methylpyridine-2-carbox-amide	412
5		N-methyl-4-{[2-(phenylamino)-1H-benzimidazol-6-yl]oxy}-pyridine-2-carboxamide	360
6		4-[(2-{[4-bromo-2-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methyl-pyridine-2-carboxamide	508

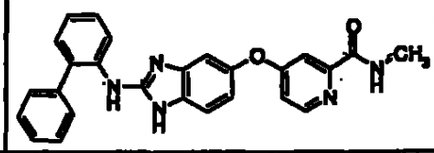
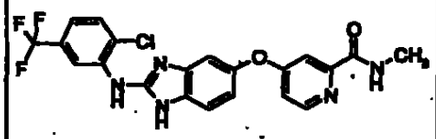
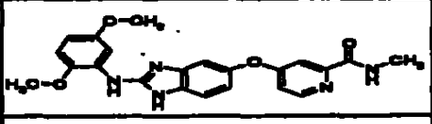
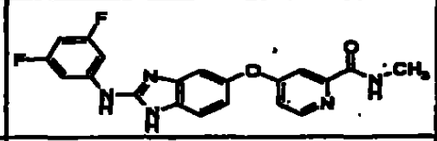
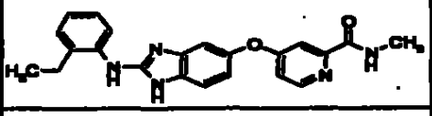
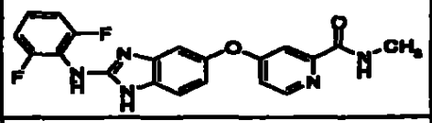
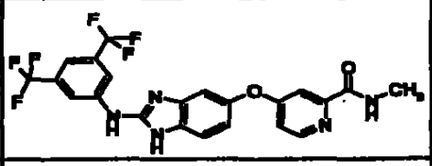
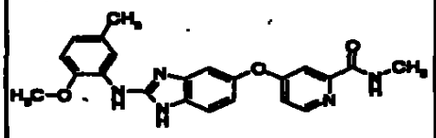
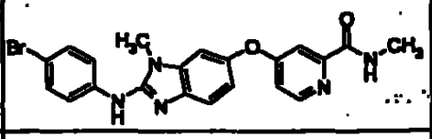
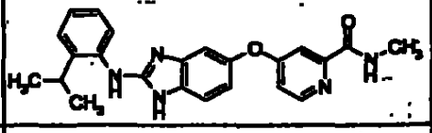
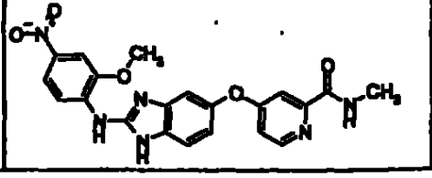
Example	Structure	Name	MH+
7		N-methyl-4-({2-[(2-methylpropyl)-amino]-1H-benzimidazol-6-yl}-oxy)pyridine-2-carboxamide	340
8		4-[(2-{[4-(dimethylamino)-naphthalen-1-yl]amino}-1H-benzimidazol-6-yl)oxy]-N-methyl-pyridine-2-carboxamide	453
9		N-methyl-4-({2-[(4-nitrophenyl)-amino]-1H-benzimidazol-6-yl}-oxy)pyridine-2-carboxamide	405
10		N-methyl-4-({2-[(phenylcarbonyl)-amino]-1H-benzimidazol-6-yl}-oxy)pyridine-2-carboxamide	388
11		N-methyl-4-({2-[(phenylmethyl)-amino]-1H-benzimidazol-6-yl}-oxy)pyridine-2-carboxamide	374
12		methyl 4-{[6-({2-[(methylamino)-carbonyl]pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}benzoate	418
13		4-({2-[(4-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methyl-pyridine-2-carboxamide	394

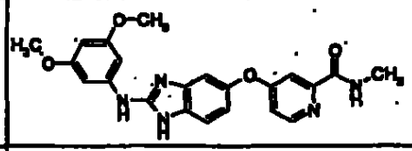
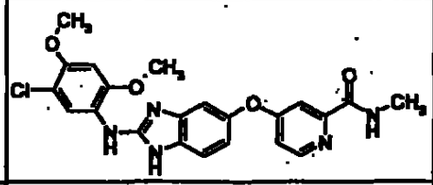
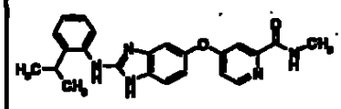
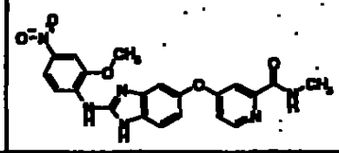
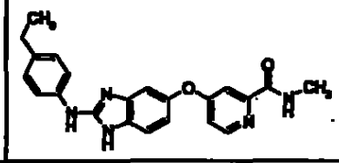
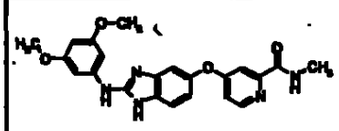
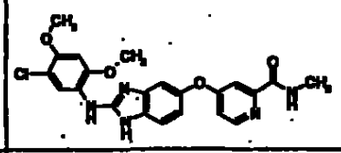
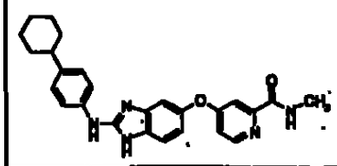
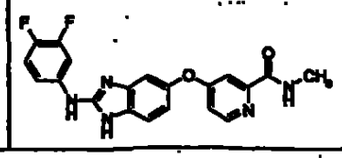
Example	Structure	Name	MH+
14		4-[(2-{[2-(ethyloxy)phenyl]-amino}-1H-benzimidazol-6-yl)-oxy]-N-methylpyridine-2-carboxamide	404
15		N-methyl-4-({2-[(2-morpholin-4-ylethyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide	397
16		4-({2-[(4-iodophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methyl-pyridine-2-carboxamide	486
17		N-methyl-4-[(2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]pyridine-2-carboxamide	428
18		4-({2-[(furan-2-ylmethyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide	364
19		4-({2-[(4-bromo-3-methylphenyl)-amino]-1H-benzimidazol-6-yl}-oxy)-N-methylpyridine-2-carboxamide	453

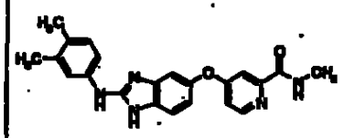
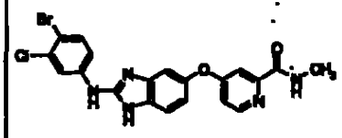
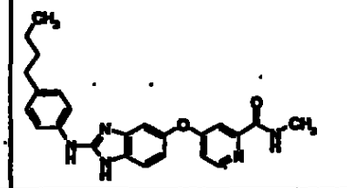
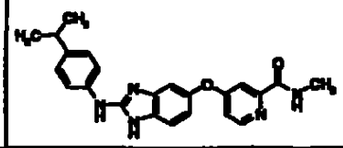
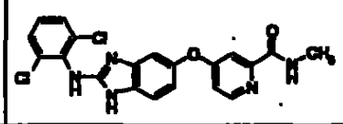
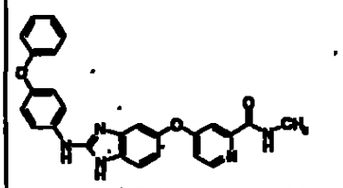
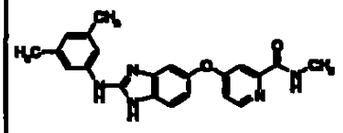
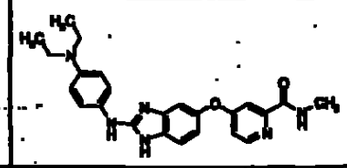
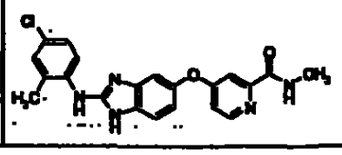
Example	Structure	Name	MH+
20		4-({2-[(4-acetylphenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methyl-pyridine-2-carboxamide	402
21		N-methyl-4-({2-[(2,4,6-trimethyl-phenyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide	402
22		4-[(2-{[4-(1,1-dimethylethyl)-phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide	416
23		4-({2-[(2-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide	440
24		4-({2-[(3-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide	440
25		4-({2-[(2-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methyl-pyridine-2-carboxamide	394

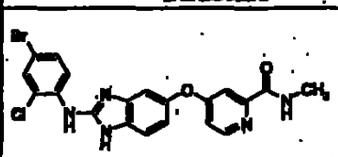
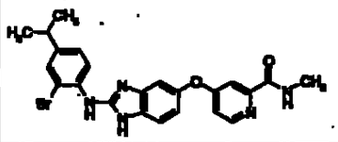
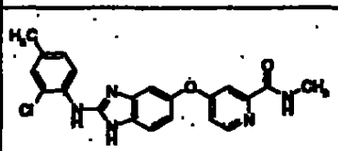
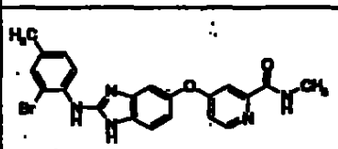
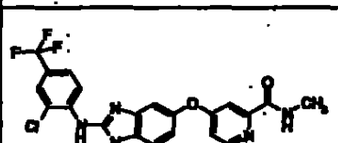
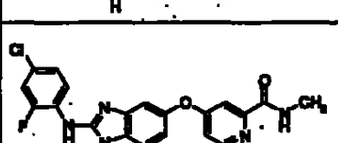
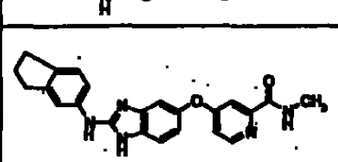
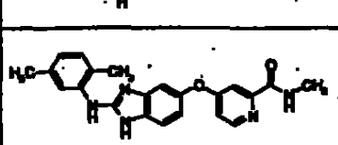
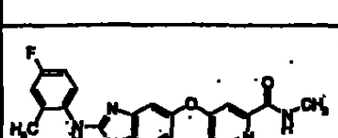
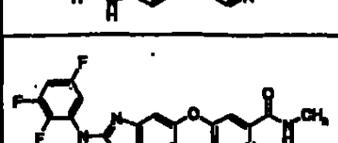
Example	Structure	Name	MH+
26		methyl 3-{[6-({2-[(methylamino)-carbonyl]pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}-thiophene-2-carboxylate	424
27		4-({2-[(4-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-{(3R,5R)-5-[(methyloxy)methyl]-pyrrolidin-3-yl}pyridine-2-carboxamide	539
28		(4-{2-[(2,5-difluorophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	395.3
29		(4-{2-[(2,4-difluorophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	395.3
30		N-methyl[4-(2-{[2-(trifluoro-methyl)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]-carboxamide	427.3
31		(4-{2-[(3,4-dichlorophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	428.2
32		N-methyl(4-{2-[(2-methylthio-phenyl)amino]benzimidazol-5-yloxy}(2-pyridyl))carboxamide	405.4
33		N-methyl(4-{2-[(4-methylthio-phenyl)amino]benzimidazol-5-yloxy}(2-pyridyl))carboxamide	405.4

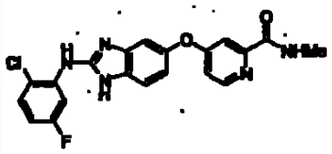
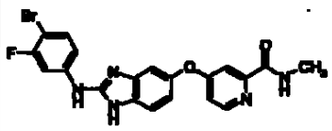
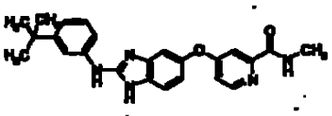
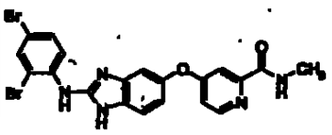
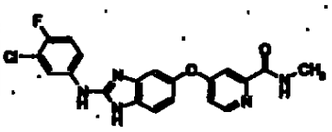
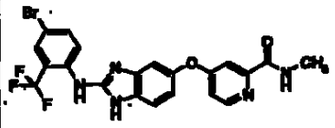
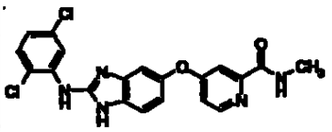
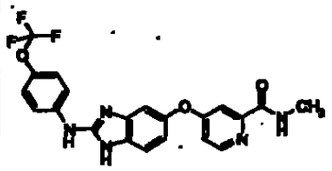
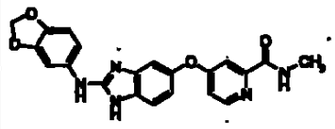
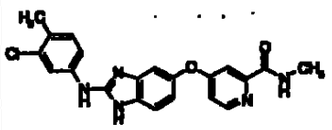
Example	Structure	Name	MH+
34		(4-{2-[(2-methoxyphenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	389.4
35		(4-{2-[(2-fluorophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	377.3
36		N-methyl(4-{2-[(4-sulfamoyl-phenyl)amino]benzimidazol-5-yloxy}(2-pyridyl))carboxamide	438.4
37		N-methyl[4-(2-{[2-(trifluoro-methoxy)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]-carboxamide	443.3
38		(4-{2-[(3,4-dimethoxyphenyl)-amino]benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	419.4
39		[4-(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide.	445.3
40		(4-{2-[(2,4-dichlorophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	428.2
41		N-methyl[4-(2-{[3-(trifluoro-methyl)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]-carboxamide	427.3
42		(4-{2-[(3-methoxyphenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	389.4

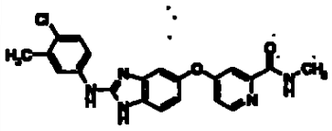
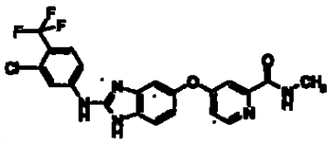
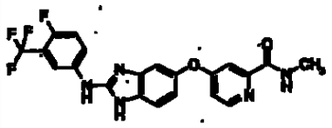
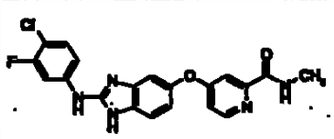
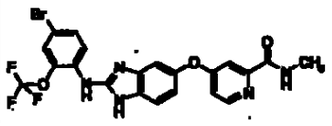
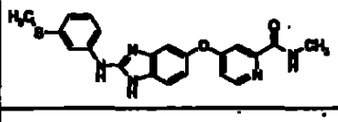
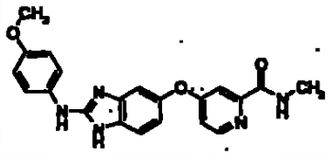
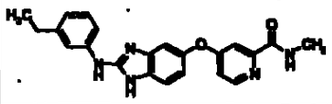
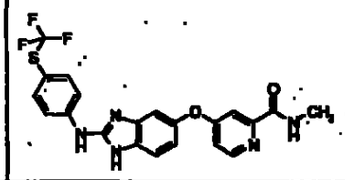
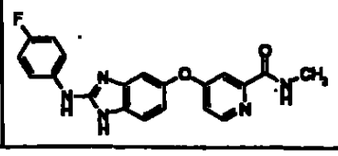
Example	Structure	Name	MH+
43		N-methyl(4-{2-[(2-phenylphenyl)-amino]benzimidazol-5-yloxy}(2-pyridyl))carboxamide	435.4
44		[4-(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide	461.8
45		(4-{2-[(2,5-dimethoxyphenyl)-amino]benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	419.4
46		(4-{2-[(3,5-difluorophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	395.3
47		(4-{2-[(2-ethylphenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	387.4
48		(4-{2-[(3,5-difluorophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	395.4
49		[4-(2-{[3,5-bis(trifluoromethyl)-phenyl]amino}benzimidazol-5-yloxy)(2-pyridyl)]-N-methyl-carboxamide	495.4
50		(4-{2-[(2-methoxy-5-methylphenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	403.4
51		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-6-yloxy}(2-pyridyl))-N-methylcarboxamide	452.3
52		N-methyl[4-(2-{[2-(methylethyl)-phenyl]amino}benzimidazol-5-yloxy)(2-pyridyl)]carboxamide	401.4
53		(4-{2-[(2-methoxy-4-nitrophenyl)-amino]benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	434.4

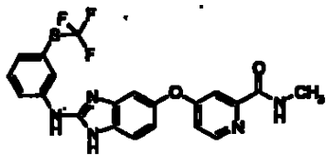
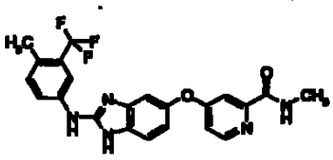
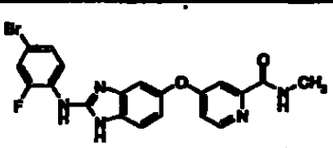
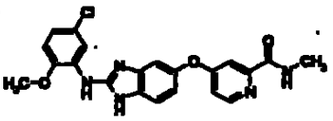
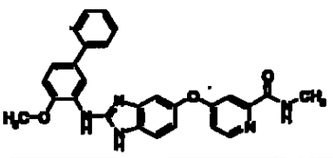
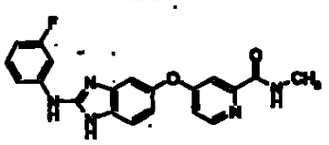
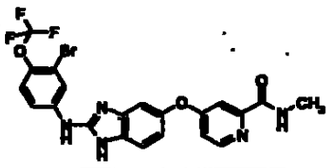
Example	Structure	Name	MH+
54		(4-{2-[(3,5-dimethoxyphenyl)-amino]benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	420.1
55		(4-{2-[(5-chloro-2,4-dimethoxy-phenyl)amino]benzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	454.1
56		N-methyl-4-[(2-{[2-(1-methyl-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	402.5
57		N-methyl-4-[(2-{[2-(methyloxy)-4-nitrophenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	435.4
58		4-({2-[(4-ethylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	388.4
59		4-[(2-{[3,5-bis(methyloxy)phenyl]-amino}-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	420.4
60		4-[(2-{[5-chloro-2,4-bis(methyl-oxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	454.9
61		4-({2-[(4-cyclohexylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	442.5
62		4-({2-[(3,4-difluorophenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	396.4

Example	Structure	Name	MH+
63		4-({2-[(3,4-dimethylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	388.4
64		4-({2-[(4-bromo-3-chlorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	473.7
65		4-({2-[(4-butylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	416.5
66		N-methyl-4-[(2-{[4-(1-methyl-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	402.5
67		4-({2-[(2,6-dichlorophenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	429.3
68		N-methyl-4-[(2-{[4-(phenyloxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	452.5
69		4-({2-[(3,5-dimethylphenyl)-amino]-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	388.4
70		4-[(2-{[4-(diethylamino)phenyl]-amino}-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	431.5
71		4-({2-[(4-chloro-2-methylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	408.9

Example	Structure	Name	MH+
72		4-({2-[(4-bromo-2-chlorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	473.7
73		4-[(2-{[2-bromo-4-(1-methyl-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	481.4
74		4-({2-[(2-chloro-4-methylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	408.9
75		4-({2-[(2-bromo-4-methylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	453.3
76		4-[(2-{[2-chloro-4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	462.8
77		4-({2-[(4-chloro-2-fluorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	412.8
78		4-{[2-(2,3-dihydro-1H-inden-5-ylamino)-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	400.5
79		4-({2-[(2,5-dimethylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	388.4
80		4-({2-[(4-fluoro-2-methylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	392.4
81		N-methyl-4-({2-[(2,3,5-trifluoro-phenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	414.4

Example	Structure	Name	MH+
82		4-({2-[(2-chloro-5-fluorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	412.8
83		4-({2-[(4-bromo-3-fluorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	457.3
84		4-[(2-{[3-(1,1-dimethylethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	416.5
85		4-({2-[(2,4-dibromophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	518.2
86		4-({2-[(3-chloro-4-fluorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	412.8
87		4-[(2-{[4-bromo-2-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	507.3
88		4-({2-[(2,5-dichlorophenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	429.3
89		N-methyl-4-{[2-({4-[(trifluoro-methyl)oxy]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	444.4
90		4-{[2-(1,3-benzodioxol-5-yl-amino)-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	404.4
91		4-({2-[(3-chloro-4-methylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	408.9

Example	Structure	Name	MH+
92		4-({2-[(4-chloro-3-methylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	408.9
93		4-[(2-{[3-chloro-4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	462.8
94		4-[(2-{[4-fluoro-3-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	446.4
95		4-({2-[(4-chloro-3-fluorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	412.8
96		4-{[2-({4-bromo-2-[(trifluoro-methyl)oxy]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	523.3
97		N-methyl-4-[(2-{[3-(methylthio)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	406.5
98		N-methyl-4-[(2-{[4-(methyloxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	390.4
99		4-({2-[(3-ethylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	388.4
100		N-methyl-4-{[2-({4-[(trifluoro-methyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	460.4
101		4-({2-[(4-fluorophenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	378.4

Example	Structure	Name	MH+
102		N-methyl-4-{[2-({3-[(trifluoro-methyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	460.4
103		N-methyl-4-[(2-{[4-methyl-3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	442.4
104		4-({2-[(4-bromo-2-fluorophenyl)-amino]-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	457.3
105		4-[(2-{[5-chloro-2-(methyloxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	424.9
106		N-methyl-4-[(2-{[4-(methyloxy)-1,1'-biphenyl-3-yl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	466.5
107		4-({2-[(3-fluorophenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	378.4
108		4-{[2-({3-bromo-4-[(trifluoro-methyl)oxy]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	523.3

Example 109

Synthesis of (4-{2-[(4-bromophenyl)amino]-benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide

Step 1. Synthesis of 2-bromo-5-methoxybenzothiazole.

A solution of bromine (3.6eq) in chloroform (.75M) was added dropwise over a period of 1 hr to a stirred suspension of 5-methoxy-2-mercaptobenzothiazole (1eq) in chloroform at 0°C. The mixture was stirred for 30 min before it was added slowly to

water and stirred for further 20 min. The mixture was filtered to remove a cream solid. The organic phase was dried and evaporated to leave a brown solid. The brown solid was dissolved in ether and filtered. The residue was washed with ether and the filtrate and washings were combined and evaporated, chromatographed (4:1 hexanes and ethyl acetate) to give the title compound as a pale yellow solid. MS: MH^+ = 244

Step 2. Synthesis of (4-bromophenyl)(5-methoxybenzothiazol-2-yl)amine

The mixture containing 2-bromo-5-methoxybenzthiazole (1eq), 4-Bromoaniline (2eq) and diisopropylethylamine was subjected to microwave in NMP at 220°C. The resultant mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried. Purification on silica gel gave the desired product. MS: MH^+ = 335

Step 3. Synthesis of 2-[(4-bromophenyl)amino]benzothiazol-5-ol

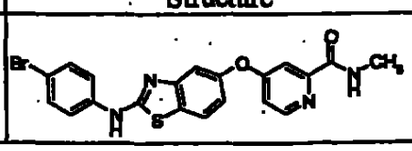
The mixture of (4-bromophenyl)(5-methoxybenzothiazol-2-yl)amine and hydrobromic acid (48%) was subjected to the microwave at 150°C for 6 mins to yield the desired product. MS: MH^+ = 321

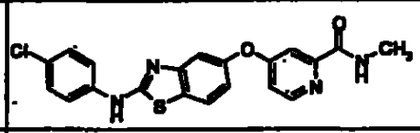
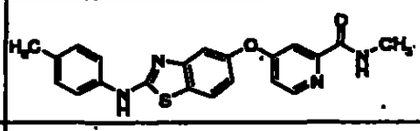
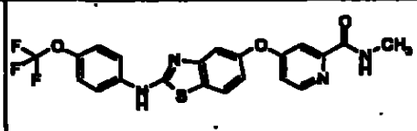
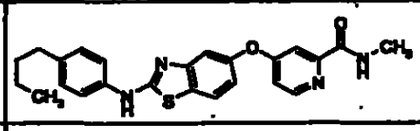
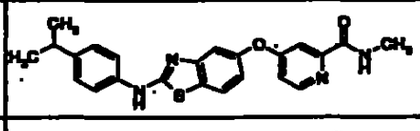
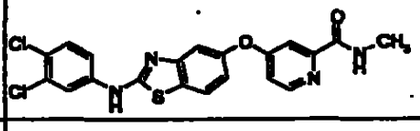
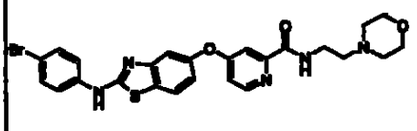
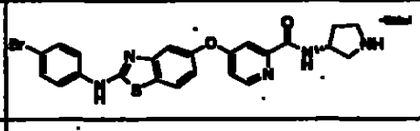
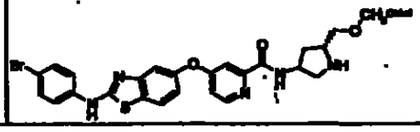
Step 4. Synthesis of (4-{2-[(4-bromophenyl)amino]benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide:

The mixture containing 2-[(4-bromophenyl)amino]benzothiazol-5-ol (1eq), Potassiumbis(trimethylsilyl)amide (4eq), was stirred in dimethylformamide for 30 min at room temperature. To this mixture was added (4-chloro(2-pyridyl)-N-methylcarboxamide (1eq) and Potassium carbonate (1.2eq) and microwaved for 6 mins at 150°C. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried, filtered and concentrated. Purification on Prep LC yielded the desired product. MS: MH^+ = 455

Each of the Examples 110-119 shown in the following Table 2 were synthesized according to the procedure described in Example 109:

Table 2

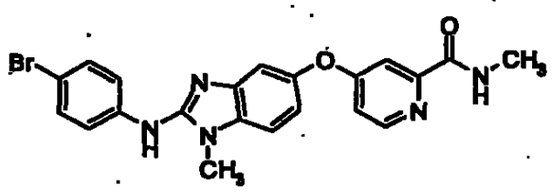
Example	Structure	Name	MH+
110		(4-{2-[(4-bromophenyl)amino]-benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	455

Example	Structure	Name	MH+
111		(4-{2-[(4-chlorophenyl)amino]-benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	411.1
112		N-methyl(4-{2-[(4-methylphenyl)-amino]benzothiazol-5-yloxy}(2-pyridyl))carboxamide	391.1
113		N-methyl[4-(2-{[4-(trifluoro-methoxy)phenyl]amino}-benzothiazol-5-yloxy)(2-pyridyl)]-carboxamide	461.1
114		(4-{2-[(4-butylphenyl)amino]-benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	433.2
115		N-methyl[4-(2-{[4-(methylethyl)-phenyl]amino}benzothiazol-5-yloxy)(2-pyridyl)]carboxamide	419.2
116		(4-{2-[(3,4-dichlorophenyl)amino]-benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	445
117		(4-{2-[(4-bromophenyl)amino]-benzothiazol-5-yloxy}(2-pyridyl))-N-(2-morpholin-4-ylethyl)-carboxamide	554.1
118		N-((3R)pyrrolidin-3-yl)(4-{2-[(4-bromophenyl)amino]benzothiazol-5-yloxy}(2-pyridyl))carboxamide	510
119		N-[(3R,5R)-5-(methoxymethyl)-pyrrolidin-3-yl](4-{2-[(4-bromo-phenyl)amino]benzothiazol	554.1

Example 120a

Synthesis of 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide

The compound 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide was synthesized as follows:



Step 1. Synthesis of 4-{[3-amino-4-(methylamino)phenyl]oxy}-*N*-methylpyridine-2-carboxamide:

A solution of 4-[(4-amino-3-nitrophenyl)oxy]-N-methylpyridine-2-carboxamide (1eq) in methylene chloride was treated with trifluoroacetic anhydride (1eq) and stirred for 10 minutes at 0°C. The mixture was quenched with saturated NaHCO3 solution. The organic layer was separated and washed with water, brine, dried and evaporated. MS: MH+=385.2.

To a solution of the trifluroacetamide (1eq) in a mixture of toluene, acetonitrile and sodium hydroxide solution (50%) was added benzyltrimethylammonium chloride (1eq) and dimethyl sulfate (1.2eq). The biphasic mixture was stirred overnight at room temperature and evaporated. The mixture was taken up in ethyl acetate, washed with water, brine, dried and evaporated. The crude product was purified by column chromatography eluting with 1:1 hexanes and ethylacetate followed by 2% triethylamine in 1:1 hexanes and ethyl acetate followed by 2% triethylamine in 1:1 hexanes and ethyl acetate to afford N-methyl-4-{[4-(methylamino)-3-nitrophenyl]oxy}pyridine-2-carboxamide as a reddish orange solid. MS: MH+ = 303.1.

The solution of nitromethylaniline in methanol was treated with 5% palladium on carbon and stirred under hydrogen atmosphere for 15 min. (until the disappearance of yellow coloration) at room temperature. The mixture was filtered and the filtrate was concentrated to provide 0.36 g of the diamine 4-{[3-amino-4-(methylamino)phenyl]oxy}-N-methylpyridine-2-carboxamide. MS: MH+ = 273.3.

Step 2. Synthesis of 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide:

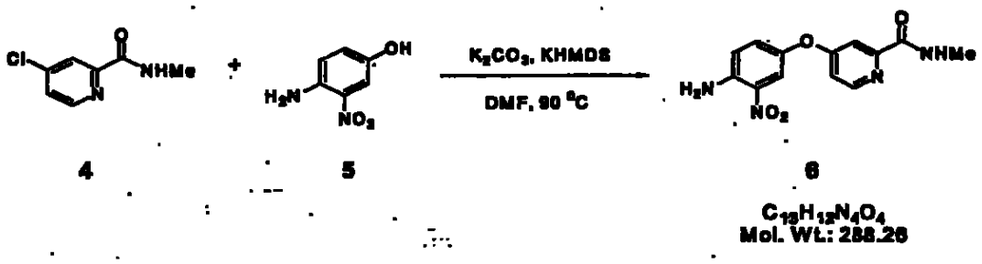
A solution of the diamine 4-{[3-amino-4-(methylamino)phenyl]oxy}-N-methylpyridine-2-carboxamide (1eq) in methanol was treated with 4-bromophenyl-isothiocyanate (1eq) and stirred at 60°C-65°C for 2 hours. The reaction mixture was cooled down to room temperature and methyl iodide (1eq) was added and stirred overnight at 60°C. The reaction was cooled to room temperature, evaporated, taken up in ethyl acetate, and washed with water and brine, dried, and evaporated under reduced

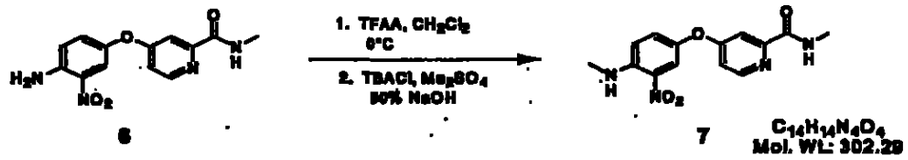
pressure. Column chromatography using a gradient solvent system of hexanes and ethyl acetate and either 1:1 methylene chloride and acetone or 5% methanol in methylene chloride yielded the product as a half white powder. MS: MH+=452.3

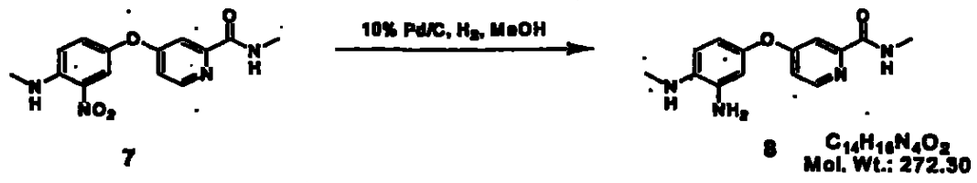
Example 120b

Alternative Synthesis of 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide

Step 1. Synthesis of *N*-methyl{4-[4-(methylamino)-3-aminophenoxy](2-pyridyl)}carboxamide:







A mixture containing 4-amino-3-nitrophenol 5 (1.0 g, 6.4 mmol), potassium bis(trimethylsilyl)amide (2.58 g, 12.8mmol) was stirred in DMF (50 ml) for 2 hours at rt. To this mixture was added (4-chloro(2-pyridyl))-*N*-methylcarboxamide 4 (1.09 g, 6.4 mmol) and potassium carbonate (0.5 g, 7.6 mmol) and stirred at 90°C overnight. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine (2 X 10 ml), dried, filtered and

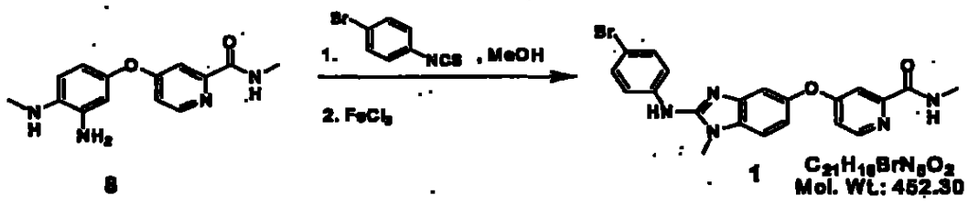
concentrated in vacuum to give brown solid. Purification on silica gel with 2% triethyl amine in 50% ethyl acetate in hexane gave 1.3 g (yield, 72%) of [4-(4-amino-3-nitrophenoxy)(2-pyridyl)]-*N*-methylcarboxamide 6 as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 5.6 Hz, 1 H), 7.99 (br s, 1 H), 7.90 (d, J = 2.7 Hz, 1 H), 7.64 (d, J = 2.7 Hz, 1 H), 7.17 (dd, J = 2.7, 9.0 Hz, 1 H), 6.95 (ddd, J = 0.7, 2.5, 5.6 Hz, 1 H), 6.89 (d, J = 9.0 Hz, 1 H), 6.18 (br s, 2 H), 3.00 (d, J = 5.1 Hz, 3 H); mp 208-210 °C dec; LCMS *m/z* 289.2 (MH^+), t_R = 1.92 min.

A 500 mL three neck round bottom flask fitted with a mechanical stirrer was charged with nitroaniline 6 (10.0 g, 34.8 mmol) and CH_2Cl_2 (175 ml). The resulting suspension was cooled to 0°C and TFAA (9.5 mL, 14.1 g, 67.0 mmol) was added over 16 h while allowing the cooling bath to expire.[2] After the reaction was judged complete by TLC,[3] TBACl (5.2 g, 17.5 mmol)[4] and dimethyl sulfate (6.7 mL, 8.9 g, 70.0 mmol) were added followed by 50% aqueous NaOH solution (140 mL). The resulting reaction mixture was cooled with an ice bath, and stirred vigorously for 1.5 h at rt.[3,5,6] The reaction was then poured over ice water and the resulting phases were partitioned and separated. The aqueous phase was extracted with CH_2Cl_2 (3 X 100 mL) and the combined organic layers were washed with brine (2 X 100 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by recrystallization (1:3 ethanol-water) to give 8.36 g (27.7 mmol, 79%) of 7 as fine red needles: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (dd, J = 0.5, 4.9 Hz, 1 H), 8.07 (br d, J = 3.7 Hz, 1 H), 7.98 (br s, 1 H), 7.95 (d, J = 2.9 Hz, 1 H), 7.62 (dd, J = 0.5, 2.9 Hz, 1 H), 7.27 (ddd, J = 0.5, 2.9, 9.3 Hz, 1 H), 6.98 (dd, J = 2.7, 5.6 Hz, 1 H), 6.92 (d, J = 9.3 Hz, 1 H), 3.07 (d, J = 5.1 MHz, 3 H), 3.00 (d, J = 5.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 164.6, 152.6, 150.0, 144.8, 142.2, 130.6, 118.9, 115.5, 114.2, 109.7, 30.2, 26.4; mp 164-166 °C. LCMS *m/z* 303.4 (MH^+), t_R = 2.37 min.

A suspension of nitroaniline 7 (5.0 g, 16.5 mmol) in methanol was sparged with N_2 for 20 min after which 10% Pd/C (0.88 g, 0.8 mmol) was added. The reaction was purged with H_2 and maintained under a H_2 atmosphere overnight at room temperature. The reaction was purged with N_2 and filtered through Celite. The collected solids were washed with EtOAc (3 X 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to afford 4.35 g (16.0 mmol, 97%) of an off white solid as 8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 5.5 Hz, 1 H), 7.99 (br s, 1 H), 7.67 (d, J = 2.5 Hz, 1 H), 6.91 (dd, J = 2.5, 5.5 Hz, 1 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.53 (dd, J = 2.5, 8.5 Hz, 1 H),

6.44 (d, J = 2.5 Hz, 1 H), 2.98 (d, J = 5.2 Hz, 3 H), 2.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 164.9, 152.2, 149.6, 146.0, 136.6, 136.3, 114.0, 112.3, 112.0, 110.2, 109.0, 31.6, 26.5; mp 153-156°C dec.; LCMS *m/z* 273.3 (MH^+), t_R = 1.66 min.

Step 2. Synthesis of (4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-*N*-methylcarboxamide:

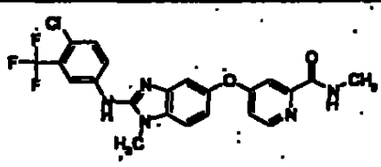
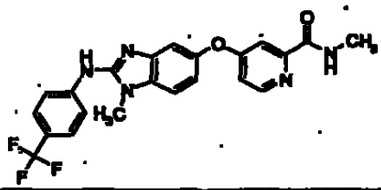
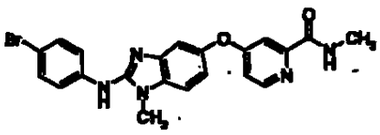
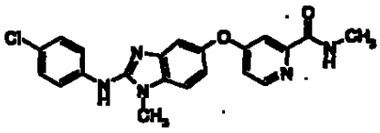
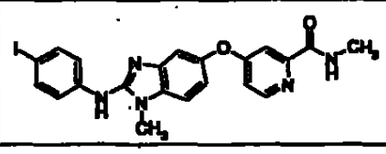
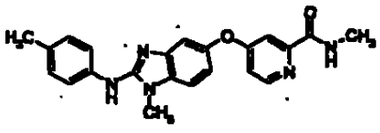
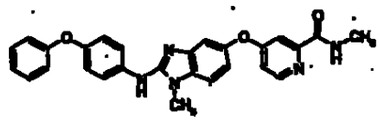
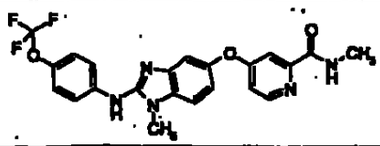
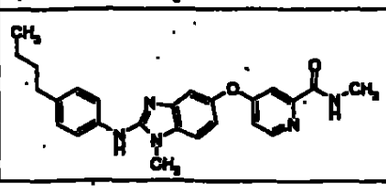


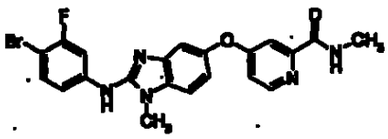
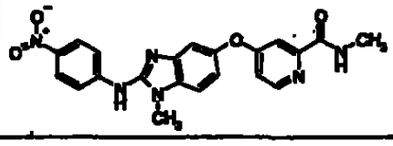
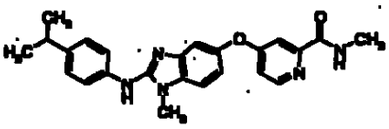
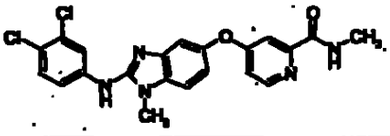
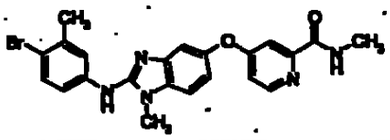
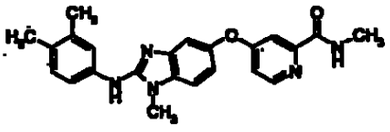
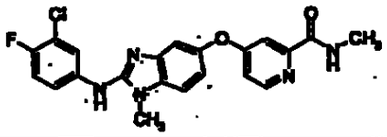
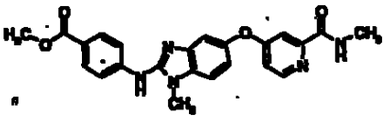
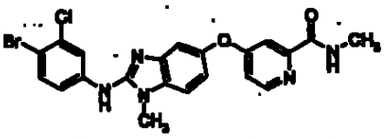
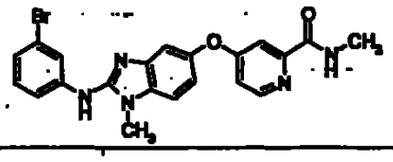
A 250 mL round bottom flask was charged with 4-bromophenylisothiocyanate[1] (2.17 g, 10.1 mmol), diamine 8 (2.74 g, 10.1 mmol), and MeOH (40 mL) and the reaction was maintained at rt overnight. Ferric chloride (2.43 g, 15 mmol) was added and the resulting red reaction mixture was stirred overnight. The reaction was partitioned with EtOAc (100 mL) and water (100 mL), and filtered through Celite. The layers were separated and the aqueous phase was neutralized (pH = 7) with saturated Na_2CO_3 solution. The resulting aqueous phase was extracted with EtOAc (100 mL) and the mixture was filtered through Celite. The phases were separated and the aqueous phase was again extracted and filtered. The combined organic layers were washed with brine (250 mL), dried ($MgSO_4$), and concentrated to give a brown solid. The crude residue was purified by trituration in hot toluene to furnish 2.22 g (4.95 mmol, 49%) of a tan solid as 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 5.8 Hz, 1 H), 8.07 (br d, J = 4.7 Hz, 1 H), 7.61 (d, J = 2.5 Hz, 1 H), 7.44 (app dd, J = 8.8, 20.6 Hz, 4 H), 7.05 (m, 3 H), 6.78 (dd, J = 2.2, 8.5 Hz, 1 H), 3.51 (s, 3 H), 3.00 (d, J = 5.2 Hz, 3 H); mp 251-254 °C dec.; LCMS *m/z* 452.2 (MH^+), t_R = 2.17 min.

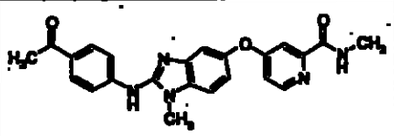
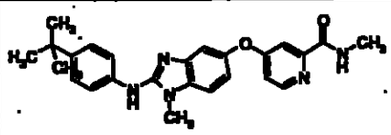
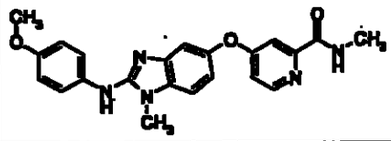
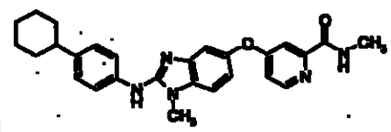
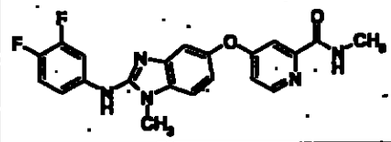
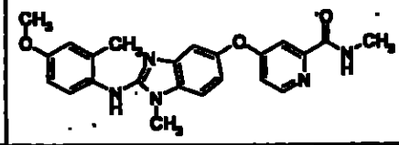
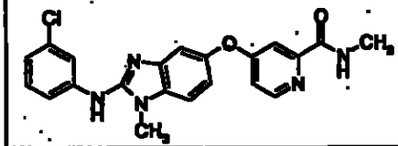
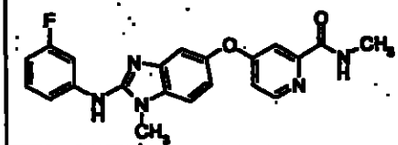
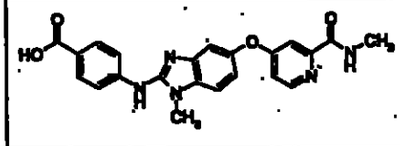
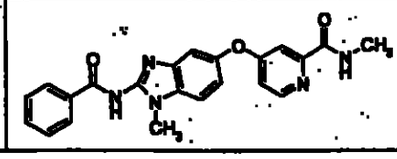
Examples 121-384

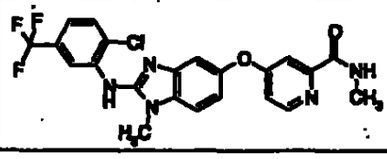
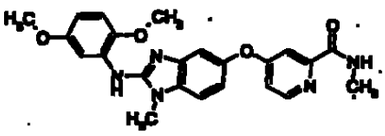
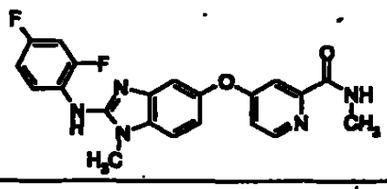
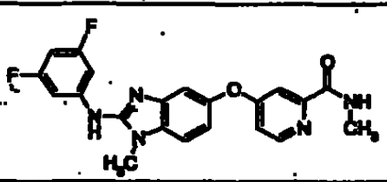
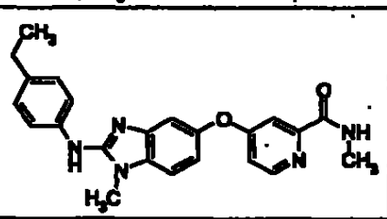
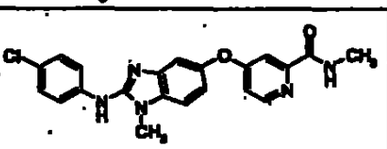
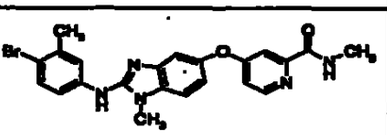
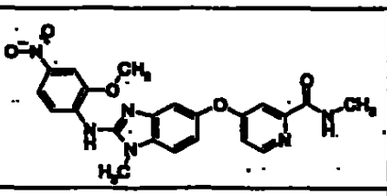
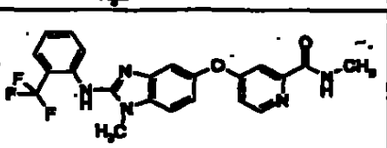
The compounds shown in the following Table 3 (Examples 121-384) were prepared from following the procedure described for Example 120a.

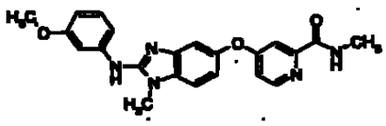
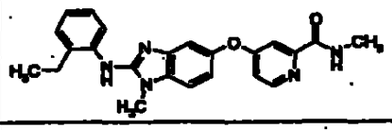
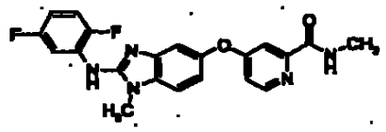
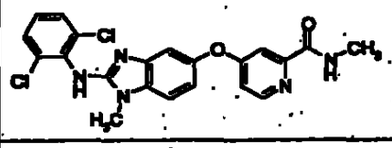
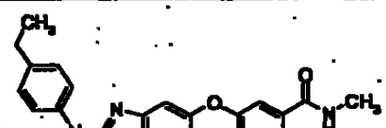
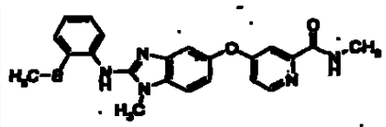
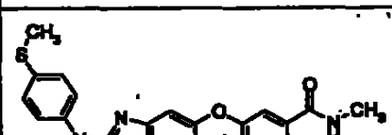
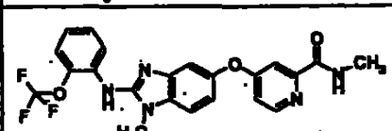
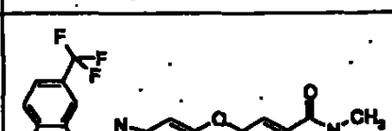
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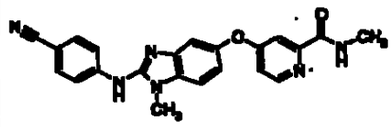
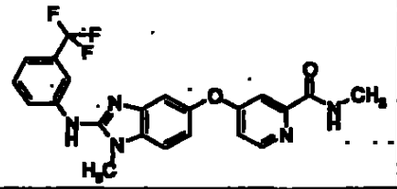
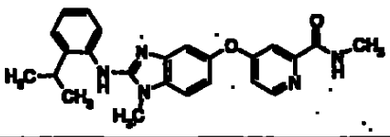
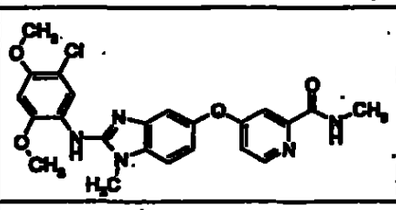
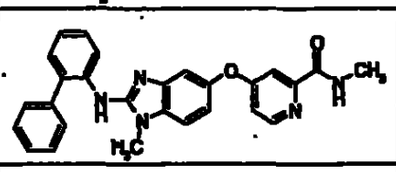
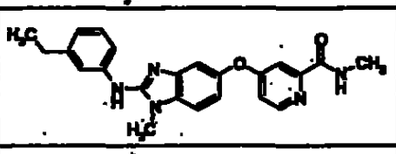
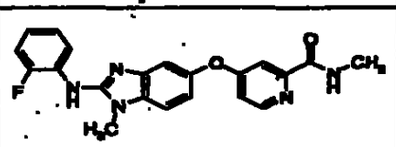
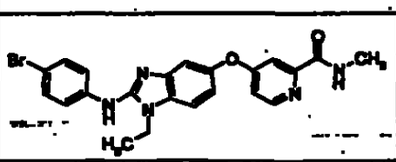
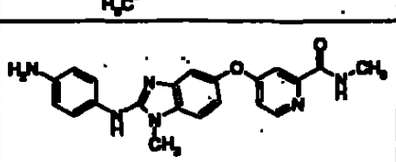
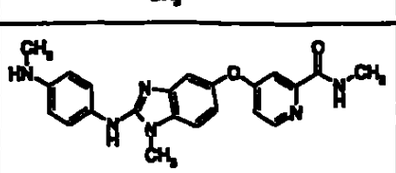
Example	Structure	Name	MH+
121		4-[(2-{[4-chloro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	476.1
122		N-methyl-4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	442
123		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yl-oxy}(2-pyridyl))-N-methyl-carboxamide	452.0
124		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarbox-amide	408.1
125		(4-{2-[(4-iodophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	500.1
126		N-methyl(4-{1-methyl-2-[(4-methylphenyl)amino]benzimidaz ol-5-yloxy}(2-pyridyl))carbox-amide	388.2
127		N-methyl(4-{1-methyl-2-[(4-phenoxyphenyl)amino]benzimid azol-5-yloxy}(2-pyridyl))-carboxamide	466.2
128		N-methyl[4-(1-methyl-2-{[4-(trifluoromethoxy)phenyl]amino }benzimidazol-5-yloxy)(2-pyridyl)]carboxamide	458.2
129		(4-{2-[(4-butylphenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	430.2

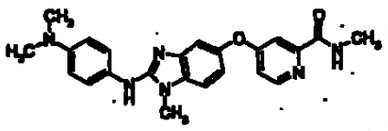
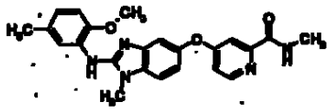
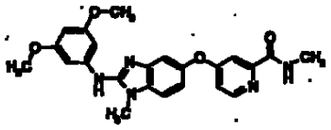
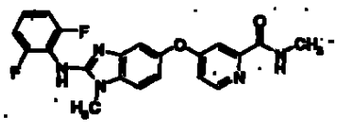
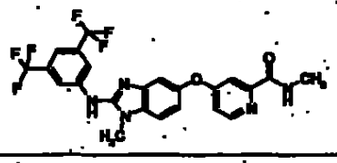
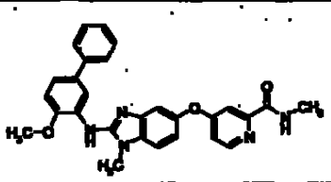
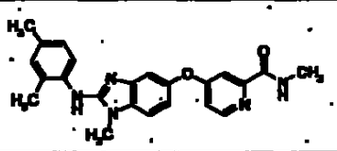
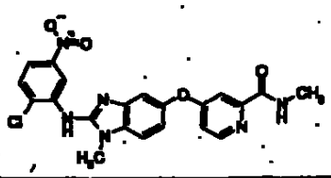
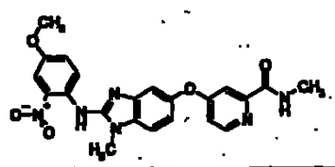
Example	Structure	Name	MH+
130		(4-{2-[(4-bromo-3-fluoro-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	470.1
131		N-methyl(4-{1-methyl-2-[(4-nitrophenyl)amino]benzimidazol-5-yloxy}(2-pyridyl))-carboxamide	419.2
132		N-methyl[4-(1-methyl-2-{[4-(methylethyl)phenyl]amino}benzimidazol-5-yloxy)(2-pyridyl)]-carboxamide	416.3
133		(4-{2-[(3,4-dichlorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	442.1
134		(4-{2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	466.1
135		(4-{2-[(3,4-dimethylphenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	402.2
136		(4-{2-[(3-chloro-4-fluoro-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	426.1
137		methyl 4-({1-methyl-5-[2-(N-methylcarbamoyl)(4-pyridyl-oxy)]benzimidazol-2-yl}amino)-benzoate	432.2
138		(4-{2-[(4-bromo-3-chloro-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	486.0
139		(4-{2-[(3-bromophenyl)amino]-1-methylbenzimidazol-5-yl-oxy}(2-pyridyl))-N-methyl-carboxamide	452.1

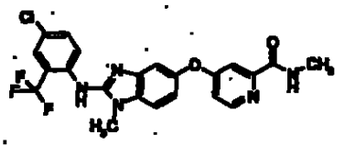
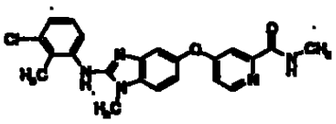
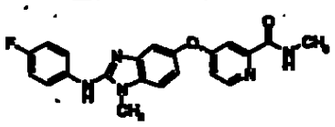
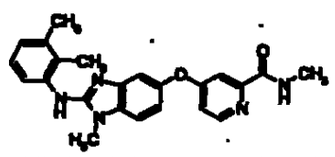
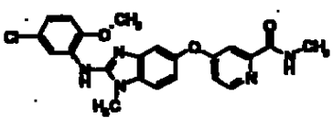
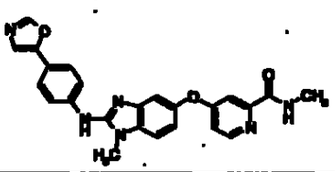
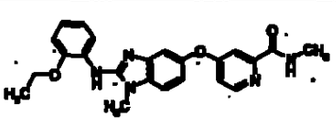
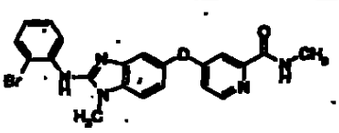
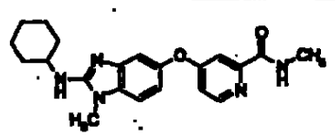
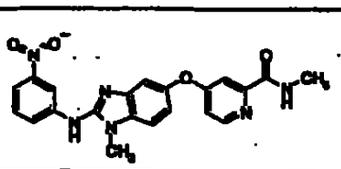
Example	Structure	Name	MH+
140		(4-{2-[(4-acetylphenyl)amino]-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide	416.2
141		[4-(2-{[4-(tert-butyl)phenyl]-amino}-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide	430.2
142		(4-{2-[(4-methoxyphenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	404.2
143		(4-{2-[(4-cyclohexylphenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	456.2
144		(4-{2-[(3,4-difluorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	410.2
145		(4-{2-[(4-methoxy-2-methylphenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	418.2
146		(4-{2-[(3-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	408.1
147		(4-{2-[(3-fluorophenyl)amino]-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide	392.2
148		4-({1-methyl-5-[2-(N-methylcarbamoyl)(4-pyridyloxy)]-benzimidazol-2-yl}amino)-benzoic acid	418.2
149		N-methyl{4-[1-methyl-2-(phenylcarbonylamino)-benzimidazol-5-yloxy](2-pyridyl)}carboxamide	402.2

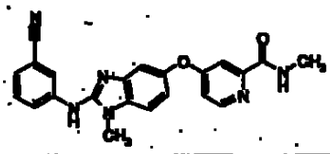
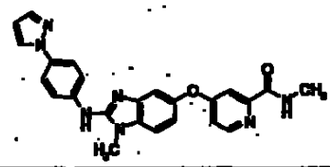
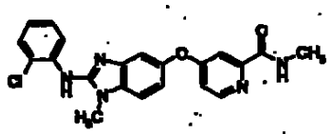
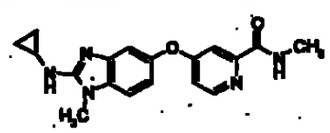
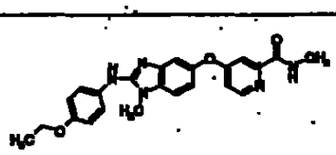
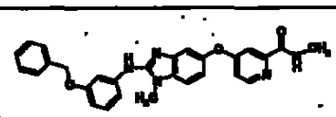
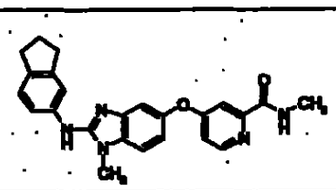
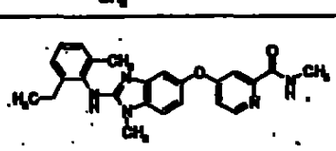
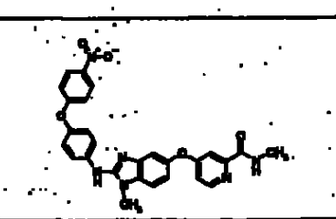
Example	Structure	Name	MH+
150		[4-(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide	476.1
151		(4-{2-[(2,5-dimethoxyphenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	434.2
152		(4-{2-[(2,4-difluorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	410.2
153		(4-{2-[(3,5-difluorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	410.2
154		(4-{2-[(4-ethylphenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	402.2
155		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarbox-amide	408.1
156		(4-{2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	466.1
157		(4-{2-[(2-methoxy-4-nitro-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	448.4
158		N-methyl[4-(1-methyl-2-{[2-(tri-fluoromethyl)phenyl]amino}ben zimidazol-5-yloxy)(2-pyridyl)]-carboxamide	441.4

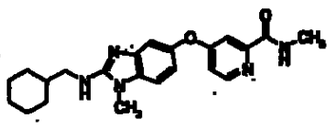
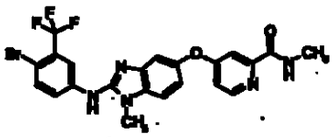
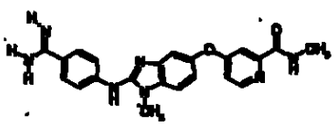
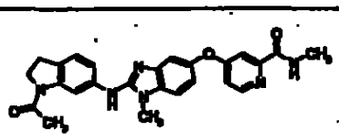
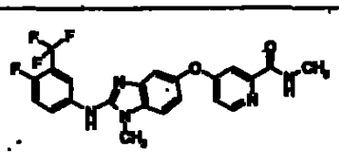
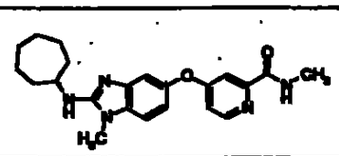
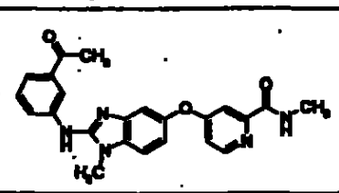
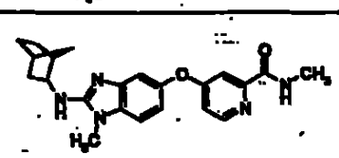
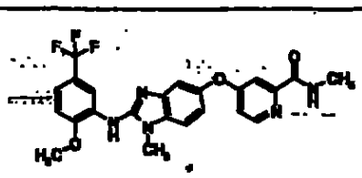
Example	Structure	Name	MH+
159		(4-{2-[(3-methoxyphenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methy-lcarboxamide	403.4
160		(4-{2-[(2-ethylphenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	401.4
161		(4-{2-[(2,5-difluorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	409.3
162		(4-{2-[(2,6-dichlorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methyl-carboxamide	442.3
163		(4-{2-[(4-ethylphenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	388.2
164		N-methyl(4-{1-methyl-2-[(2-methylthiophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	420.1
165		N-methyl(4-{1-methyl-2-[(4-methylthiophenyl)amino]-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	420.1
166		N-methyl[4-(1-methyl-2-{[2-(trifluoromethoxy)phenyl]-amino}benzimidazol-5-yloxy)(2-pyridyl)]carboxamide	458.1
167		[4-(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide	460.1

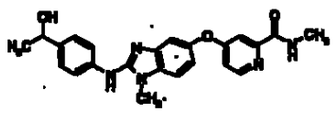
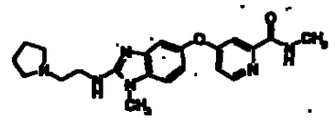
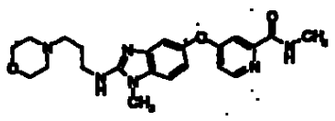
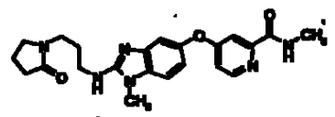
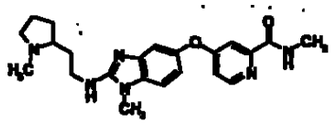
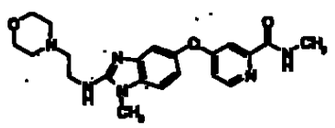
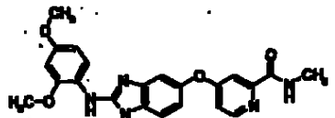
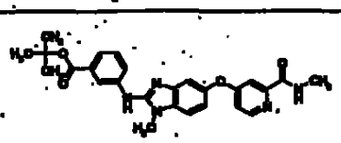
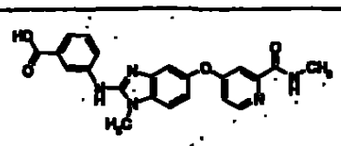
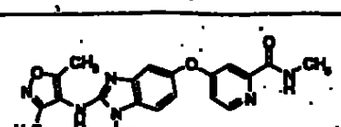
Example	Structure	Name	MH+
168		(4-{2-[(4-cyanophenyl)amino]-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methyl-carboxamide	399.1
169		N-methyl[4-(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]carboxamide	442.1
170		N-methyl[4-(1-methyl-2-{[2-(methylethyl)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]carboxamide	416.2
171		(4-{2-[(5-chloro-2,4-dimethoxy-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	468.2
172		N-methyl(4-{1-methyl-2-[(2-phenylphenyl)amino]benz-imidazol-5-yloxy}(2-pyridyl))-carboxamide	450.2
173		(4-{2-[(3-ethylphenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	402.2
174		(4-{2-[(2-fluorophenyl)amino]-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarbox-amide	392.1
175		(4-{2-[(4-bromophenyl)amino]-1-ethylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	466.1
176		(4-{2-[(4-aminophenyl)amino]-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarbox-amide	389.2
177 (synthesis as in Ex 1)		N-methyl[4-(1-methyl-2-{[4-(methylamino)phenyl]amino}-benzimidazol-5-yloxy)(2-pyridyl)]carboxamide	403.2

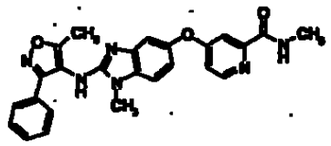
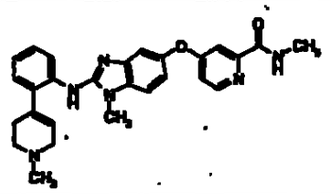
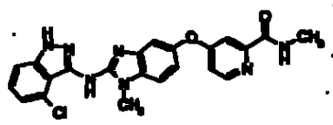
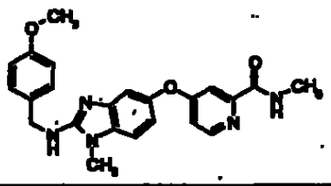
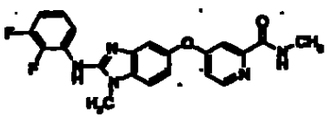
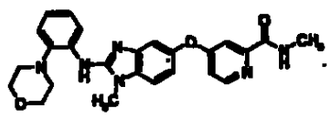
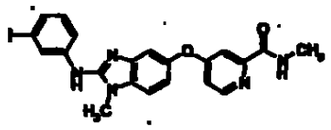
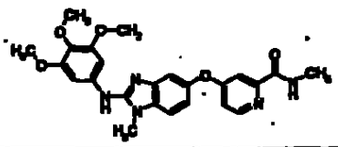
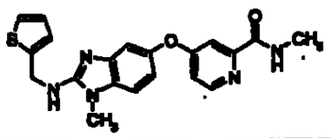
Example	Structure	Name	MH+
178 (synthesis as in Ex 1)		[4-(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide	417.2
179		N-methyl-4-[(1-methyl-2-{[5-methyl-2-(methyloxy)phenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	418.5
180		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	434.5
181		4-({2-[(2,6-difluorophenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	410.4
182		4-[(2-{[3,5-bis(trifluoromethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	510.4
183		N-methyl-4-[(1-methyl-2-{[4-(methyloxy)-1,1'-biphenyl-3-yl]-amino}-1H-benzimidazol-5-yl)-oxy]pyridine-2-carboxamide	480.5
184		4-({2-[(2,4-dimethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	402.5
185		4-({2-[(2-chloro-5-nitrophenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	453.9
186		N-methyl-4-[(1-methyl-2-{[4-(methyloxy)-2-nitrophenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	449.4

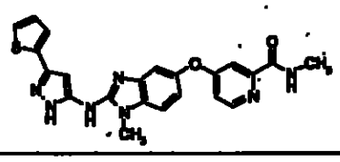
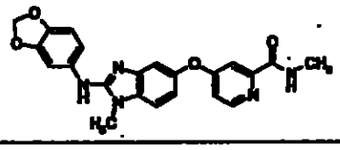
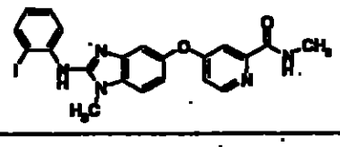
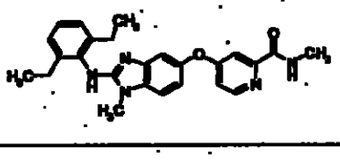
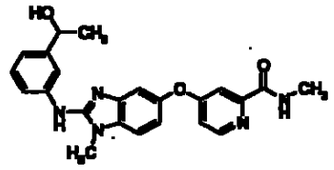
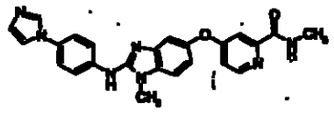
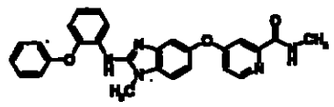
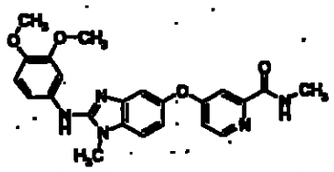
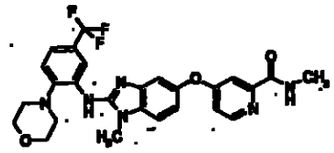
Example	Structure	Name	MH+
187		4-[(2-{[4-chloro-2-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	476.9
188		4-({2-[(3-chloro-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	422.9
189		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	392.4
190		4-({2-[(2,3-dimethylphenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	402.5
191		4-[(2-{[5-chloro-2-(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	438.9
192		N-methyl-4-[(1-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	441.5
193		4-[(2-{[2-(ethyloxy)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	418.5
194		4-({2-[(2-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	453.3
195		4-{[2-(cyclohexylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	380.5
196		N-methyl-4-({1-methyl-2-[(3-nitrophenyl)amino]-1H-benz-imidazol-5-yl}oxy)pyridine-2-carboxamide	419.4

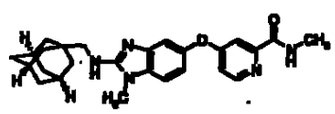
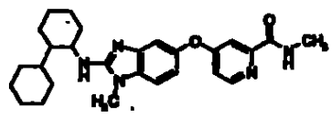
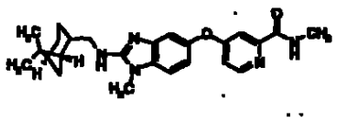
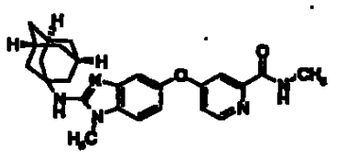
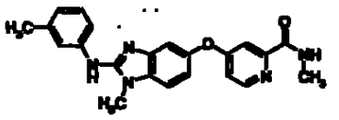
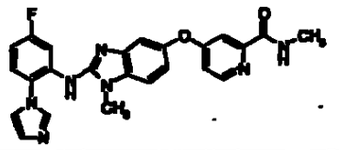
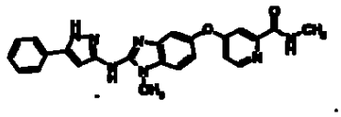
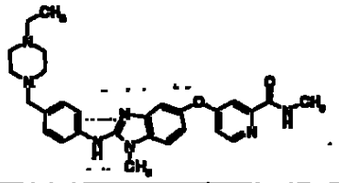
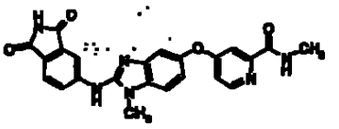
Example	Structure	Name	MH+
197		4-({2-[(3-cyanophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	399.4
198		N-methyl-4-[(1-methyl-2-{[4-(1H-pyrazol-1-yl)phenyl]-amino}-1H-benzimidazol-5-yl)-oxy]pyridine-2-carboxamide	440.5
199		4-({2-[(2-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	408.9
200		4-{[2-(cyclopropylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	338.4
201		4-[(2-{[4-(ethyloxy)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	418.5
202		N-methyl-4-{[1-methyl-2-({3-[(phenylmethyl)oxy]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	480.5
203		4-{[2-(2,3-dihydro-1H-inden-5-ylamino)-1-methyl-1H-benz-imidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	414.5
204		4-({2-[(2-ethyl-6-methylphenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	416.5
205		N-methyl-4-{[1-methyl-2-({4-[(4-nitrophenyl)oxy]phenyl}-amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	511.5

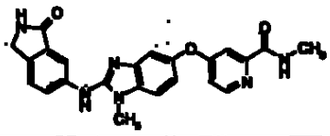
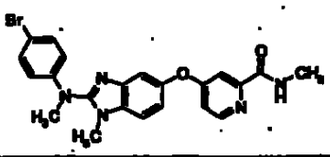
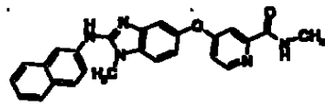
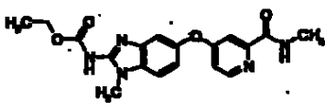
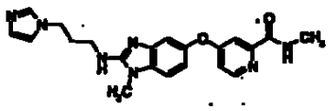
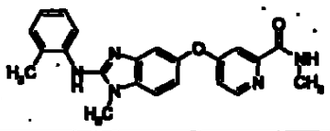
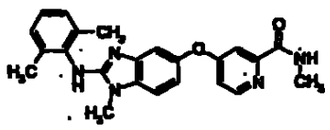
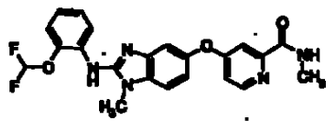
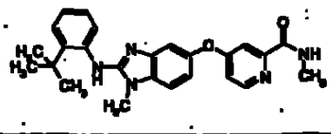
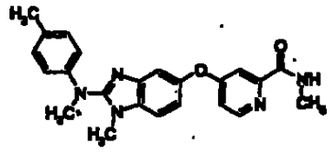
Example	Structure	Name	MH+
206		4-({2-[(cyclohexylmethyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	394.5
207		4-[(2-{[4-bromo-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	521.3
208		4-{[2-({4-[(Z)-amino(imino)-methyl]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	416.5
209		4-({2-[(1-acetyl-2,3-dihydro-1H-indol-6-yl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	457.5
210		4-[(2-{[4-fluoro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	460.4
211		4-{[2-(cycloheptylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	394.5
212		4-({2-[(3-acetylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	416.5
213		4-{[2-(bicyclo[2.2.1]hept-2-ylamino)-1-methyl-1H-benz-imidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	392.5
214		N-methyl-4-[(1-methyl-2-{[2-(methyloxy)-5-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	472.4

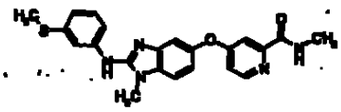
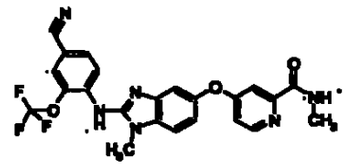
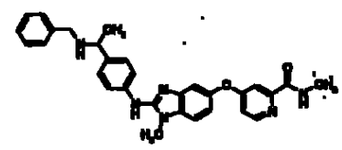
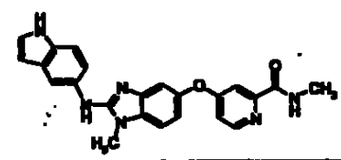
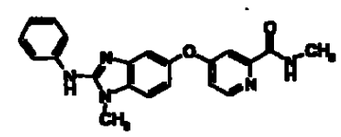
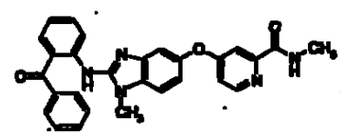
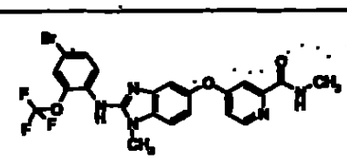
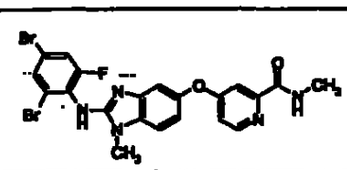
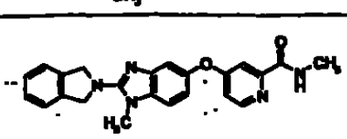
Example	Structure	Name	MH+
215		4-[(2-{[4-(1-hydroxyethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	418.5
216		N-methyl-4-({1-methyl-2-[(2-pyrrolidin-1-ylethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	395.5
217		N-methyl-4-({1-methyl-2-[(3-morpholin-4-ylpropyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	425.5
218		N-methyl-4-[(1-methyl-2-{[3-(2-oxopyrrolidin-1-yl)propyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	423.5
219		N-methyl-4-[(1-methyl-2-{[2-(1-methylpyrrolidin-2-yl)ethyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	409.5
220		N-methyl-4-({1-methyl-2-[(2-morpholin-4-ylethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	411.5
221		4-[(2-{[2,4-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	434.5
222		1,1-dimethylethyl 3-{[1-methyl-5-({2-[(methylamino)carbonyl]-pyridin-4-yl}oxy)-1H-benz-imidazol-2-yl]amino}benzoate	474.5
223		3-{[1-methyl-5-({2-[(methyl-amino)carbonyl]pyridin-4-yl}-oxy)-1H-benzimidazol-2-yl]-amino}benzoic acid	418.4
224		4-({2-[(3,5-dimethylisoxazol-4-yl)amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	393.4

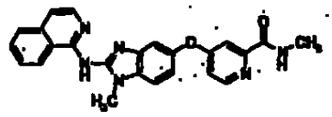
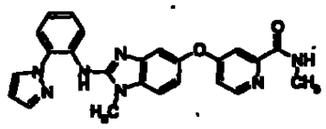
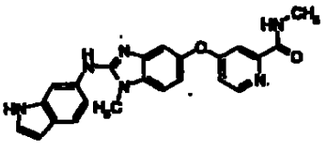
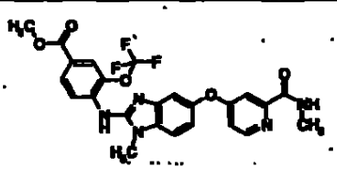
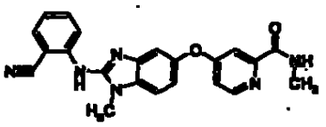
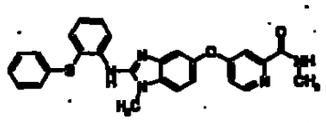
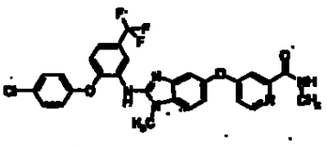
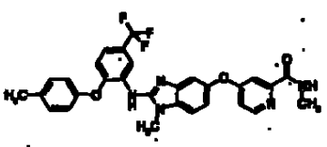
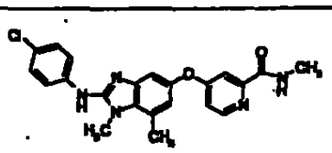
Example	Structure	Name	MH+
225		N-methyl-4-({1-methyl-2-[(5-methyl-3-phenylisoxazol-4-yl)-amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	455.5
226		N-methyl-4-[(1-methyl-2-{[2-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	469.6
227		4-({2-[(4-chloro-1H-indazol-3-yl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	448.9
228		N-methyl-4-{[1-methyl-2-({[4-(methyloxy)phenyl]methyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	418.5
229		4-({2-[(2,3-difluorophenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	410.4
230		N-methyl-4-({1-methyl-2-[(2-morpholin-4-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	459.5
231		4-({2-[(3-iodophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	500.3
232		N-methyl-4-[(1-methyl-2-{[3,4,5-tris(methyloxy)phenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	464.5
233		N-methyl-4-({1-methyl-2-[(thien-2-ylmethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	394.5

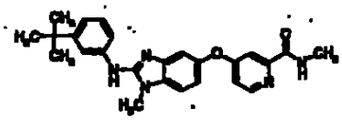
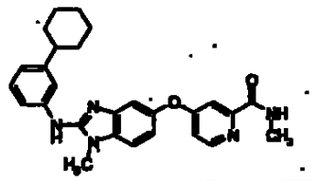
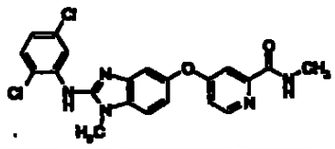
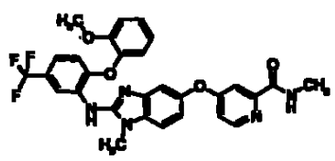
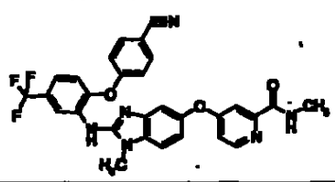
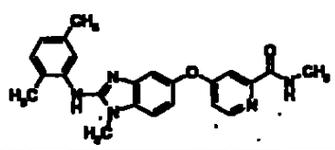
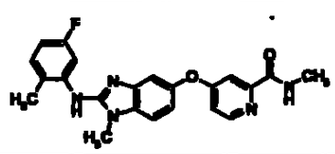
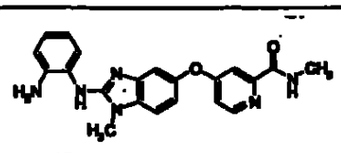
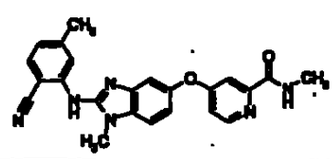
Example	Structure	Name	MH+
234		N-methyl-4-({1-methyl-2-[(3-thien-2-yl-1H-pyrazol-5-yl)-amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	446.5
235		4-{[2-(1,3-benzodioxol-5-yl-amino)-1-methyl-1H-benz-imidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	418.4
236		4-({2-[(2-iodophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	500.3
237		4-({2-[(2,6-diethylphenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N-methyl-pyridine-2-carboxamide	430.5
238		4-[(2-{[3-(1-hydroxyethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	418.5
239		4-[(2-{[4-(1H-imidazol-1-yl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	440.5
240		N-methyl-4-[(1-methyl-2-{[2-(phenyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	466.5
241		4-[(2-{[3,4-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	434.5
242		N-methyl-4-[(1-methyl-2-{[2-morpholin-4-yl-5-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	527.5

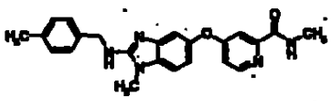
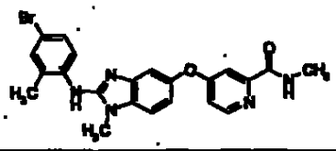
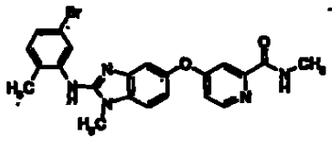
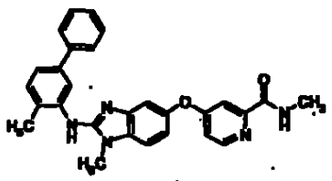
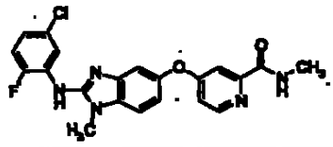
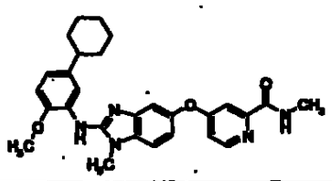
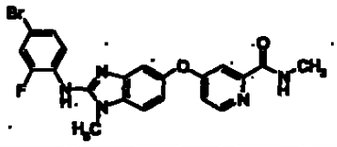
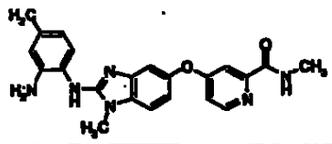
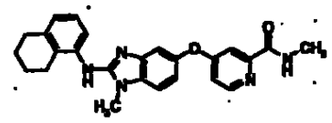
Example	Structure	Name	MH+
243		N-methyl-4-({1-methyl-2-[(tricyclo[3.3.1.1~3,7~]dec-1-ylmethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	446.6
244		4-({2-[1,1'-bi(cyclohexyl)-2-ylamino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	462.6
245		4-{[2-({[(1S,5S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-yl]methyl}-amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	434.6
246		N-methyl-4-{[1-methyl-2-(tricyclo[3.3.1.1~3,7~]dec-1-ylamino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	432.5
247		N-methyl-4-({1-methyl-2-[(3-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	388.4
248		4-[(2-{[5-fluoro-2-(1H-imidazol-1-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	458.5
249		N-methyl-4-({1-methyl-2-[(5-phenyl-1H-pyrazol-3-yl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	440.5
250		4-{[2-({4-[(4-ethylpiperazin-1-yl)methyl]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	500.6
251		4-({2-[(1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	443.4

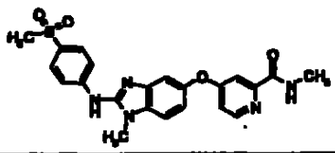
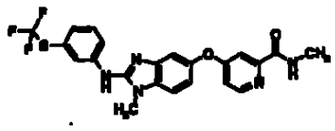
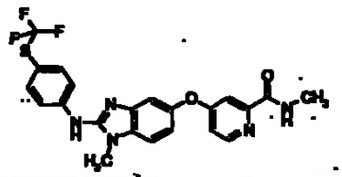
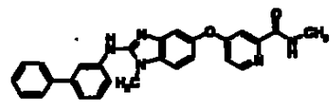
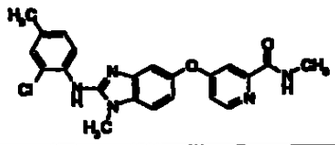
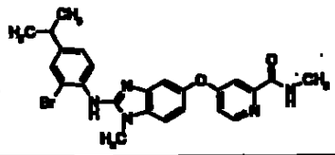
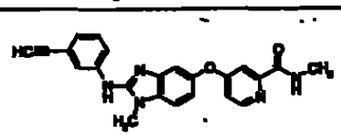
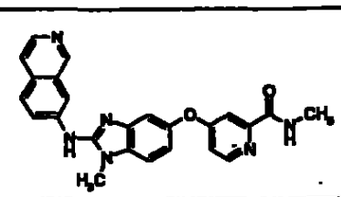
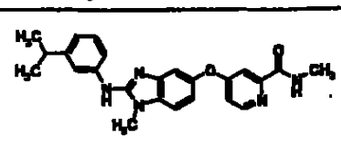
Example	Structure	Name	MH+
252		N-methyl-4-({1-methyl-2-[(3-oxo-2,3-dihydro-1H-isoindol-5-yl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	429.4
253		4-({2-[(4-bromophenyl)-(methyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	467.3
254		N-methyl-4-{[1-methyl-2-(naphthalen-2-ylamino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	424.5
255		ethyl 1-methyl-5-({2-[(methyl-amino)carbonyl]pyridin-4-yl}-oxy)-1H-benzimidazol-2-yl-carbamate	370.4
256		4-[(2-{[3-(1H-imidazol-1-yl)-propyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	406.5
257		N-methyl-4-({1-methyl-2-[(2-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	388.4
258		4-({2-[(2,6-dimethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	402.5
259		4-{[2-({2-[(difluoromethyl)-oxy]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	440.4
260		4-[(2-{[2-(1,1-dimethylethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	430.5
261		N-methyl-4-({1-methyl-2-[methyl(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	402.5

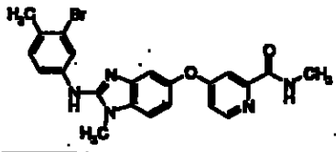
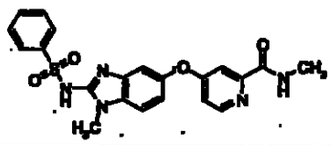
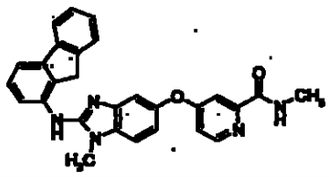
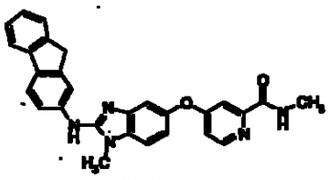
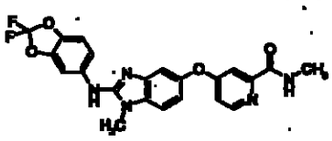
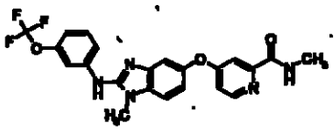
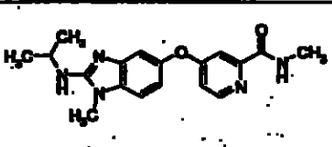
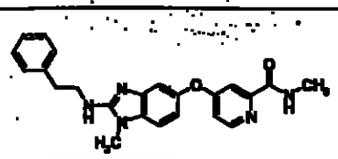
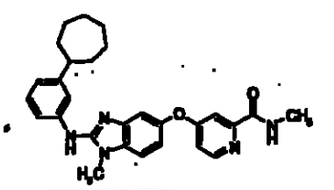
Example	Structure	Name	MH+
262		N-methyl-4-[(1-methyl-2-{[3-(methylthio)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	420.5
263		4-{[2-({4-cyano-2-[(trifluoromethyl)oxy]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	483.4
264		N-methyl-4-({1-methyl-2-[(4-{1-[(phenylmethyl)amino]-ethyl}phenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	507.6
265		4-{[2-(1H-indol-5-ylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	413.5
266		N-methyl-4-{[1-methyl-2-(phenylamino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	374.4
267		N-methyl-4-[(1-methyl-2-{[2-(phenylcarbonyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	478.5
268		4-{[2-({4-bromo-2-[(trifluoromethyl)oxy]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	537.3
269		4-({2-[(2,4-dibromo-6-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	550.2
270		4-{[2-(1,3-dihydro-2 h-isoindol-2-yl)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	400.5

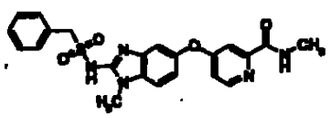
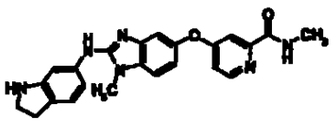
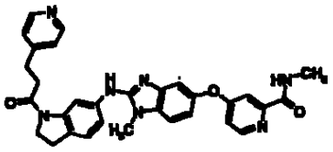
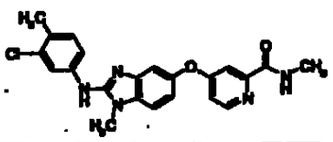
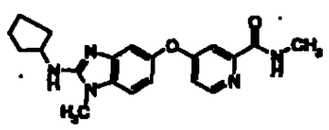
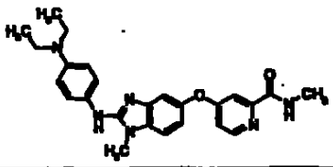
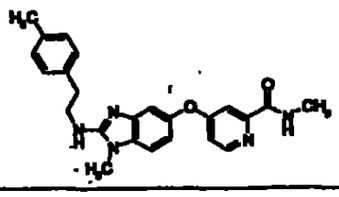
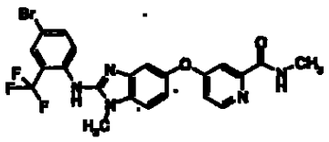
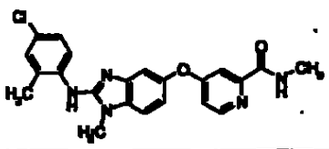
Example	Structure	Name	MH+
271		4-{[2-(isoquinolin-1-ylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	425.5
272		N-methyl-4-[(1-methyl-2-{[2-(1H-pyrazol-1-yl)phenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	440.5
273		4-{[2-(1H-indol-6-ylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	413.5
274		methyl 4-{[1-methyl-5-({2-[(methylamino)carbonyl]pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}-3-[(trifluoromethyl)-oxy]benzoate	516.4
275		4-({2-[(2-cyanophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	399.4
276		N-methyl-4-[(1-methyl-2-{[2-(phenylthio)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	482.6
277		4-[(2-{[2-[(4-chlorophenyl)oxy]-5-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	569.0
278		N-methyl-4-[(1-methyl-2-{[2-[(4-methylphenyl)oxy]-5-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	548.5
279		4-({2-[(4-chlorophenyl)amino]-1,7-dimethyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	422.9

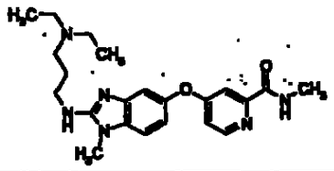
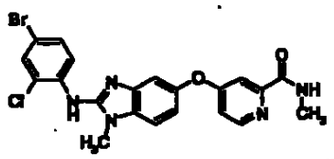
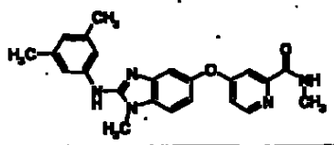
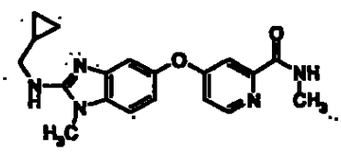
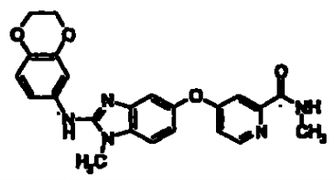
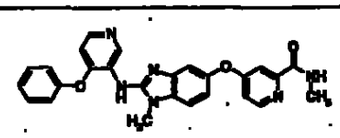
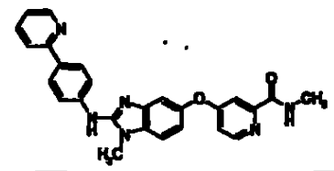
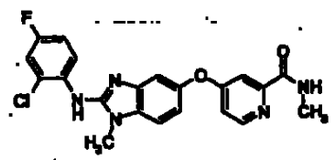
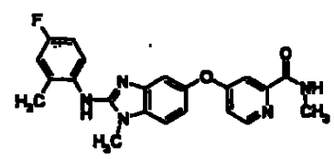
Example	Structure	Name	MH+
280		4-[(2-{[3-(1,1-dimethylethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	430.5
281		4-({2-[(3-cyclohexylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	456.6
282		4-({2-[(2,5-dichlorophenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	443.3
283		N-methyl-4-[(1-methyl-2-{[2-{[2-(methyloxy)phenyl]oxy}-5-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	564.5
284		4-[(2-{[2-[(4-cyanophenyl)oxy]-5-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	559.5
285		4-({2-[(2,5-dimethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	402.5
286		4-({2-[(5-fluoro-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	406.4
287		4-({2-[(2-aminophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	389.4
288		4-({2-[(2-cyano-5-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	413.5

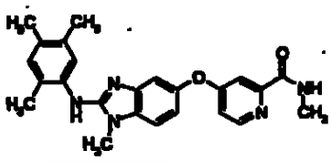
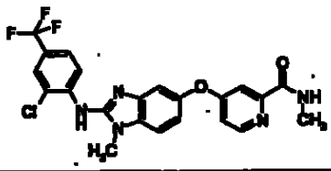
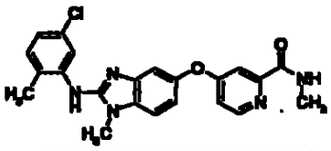
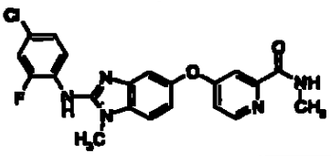
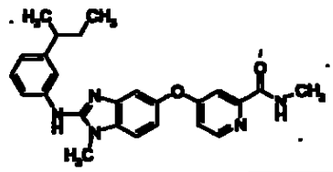
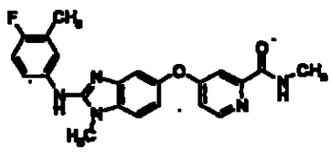
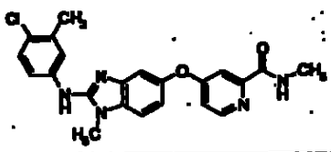
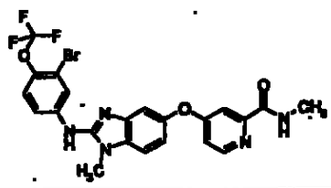
Example	Structure	Name	MH+
289		N-methyl-4-[(1-methyl-2-{[(4-methylphenyl)methyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	402.5
290		4-({2-[(4-bromo-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	467.3
291		4-({2-[(5-bromo-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	467.3
292		N-methyl-4-({1-methyl-2-[(4-methyl-1,1'-biphenyl-3-yl)-amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	464.5
293		4-({2-[(5-chloro-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	426.8
294		4-[(2-{[5-cyclohexyl-2-(methyl-oxy)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	486.6
295		4-({2-[(4-bromo-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	471.3
296		4-({2-[(2-amino-4-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	403.5
297		N-methyl-4-{[1-methyl-2-(5,6,7,8-tetrahydronaphthalen-1-ylamino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	428.5

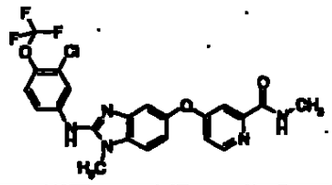
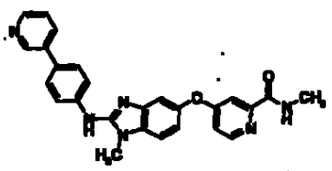
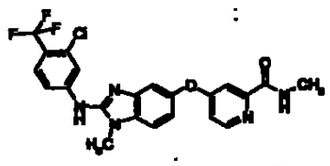
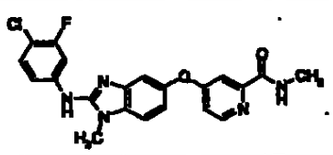
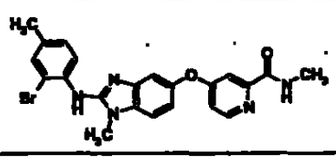
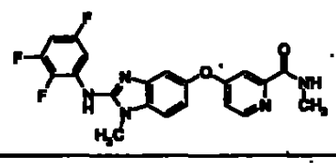
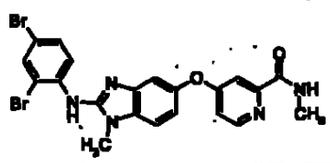
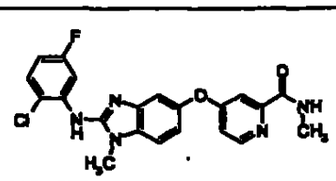
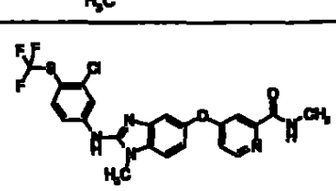
Example	Structure	Name	MH+
298		N-methyl-4-[(1-methyl-2-{[4-(methylsulfonyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	452.5
299		N-methyl-4-{[1-methyl-2-({3-[(trifluoromethyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	474.5
300		N-methyl-4-{[1-methyl-2-({4-[(trifluoromethyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	474.5
301		4-{[2-(1,1'-biphenyl-3-ylamino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	450.5
302		4-({2-[(2-chloro-4-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	422.9
303		4-[(2-{[2-bromo-4-(1-methylethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	495.4
304		4-({2-[(3-ethynylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	398.4
305		4-{[2-(isoquinolin-7-ylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	425.5
306		N-methyl-4-[(1-methyl-2-{[3-(1-methylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	416.5

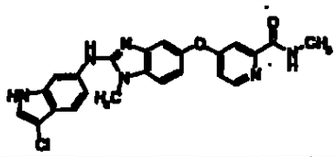
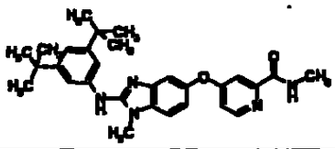
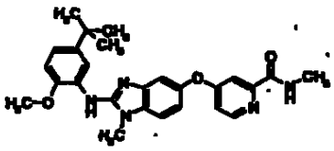
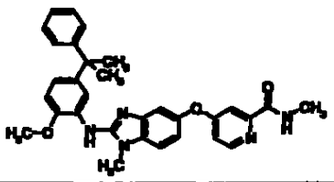
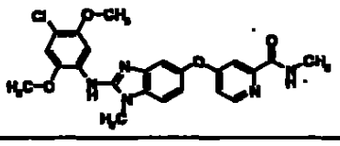
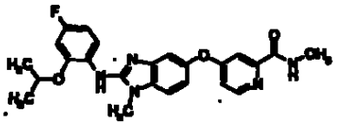
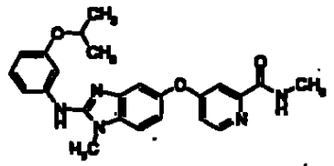
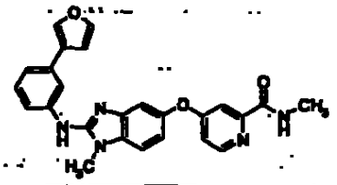
Example	Structure	Name	MH+
307		4-({2-[(3-bromo-4-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	467.3
308		N-methyl-4-({1-methyl-2-[(phenylsulfonyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	438.5
309		4-{[2-(9H-fluoren-1-ylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	462.5
310		4-{[2-(9H-fluoren-2-ylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	462.5
311		4-({2-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	454.4
312		N-methyl-4-{[1-methyl-2-({3-[(trifluoromethyl)oxy]phenyl}amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	458.4
313		N-methyl-4-({1-methyl-2-[(1-methylethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	340.4
314		N-methyl-4-({1-methyl-2-[(2-phenylethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	402.5
315		4-({2-[(3-cycloheptylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	470.6

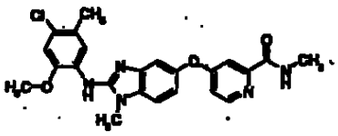
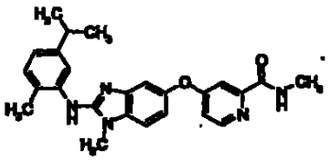
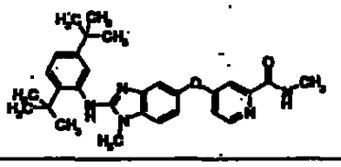
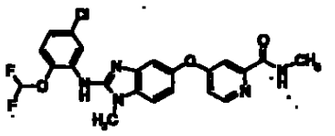
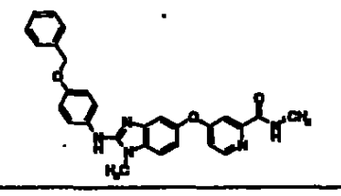
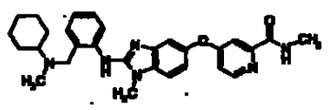
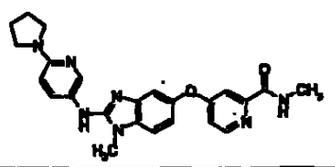
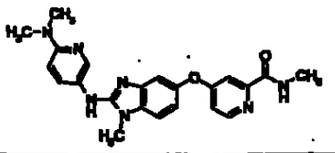
Example	Structure	Name	MH+
316		N-methyl-4-[(1-methyl-2-{[(phenylmethyl)sulfonyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	452.5
317		4-{[2-(2,3-dihydro-1H-indol-6-ylamino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	415.5
318		N-methyl-4-[(1-methyl-2-{[1-(3-pyridin-4-ylpropanoyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	548.6
319		4-({2-[(3-chloro-4-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	422.9
320		4-{[2-(cyclopentylamino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	366.4
321 (synthesis as in Ex 1)		4-[(2-{[4-(diethylamino)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	445.5
322		N-methyl-4-[(1-methyl-2-{[2-(4-methylphenyl)ethyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	416.5
323		4-[(2-{[4-bromo-2-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	521.3
324		4-({2-[(4-chloro-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	422.9

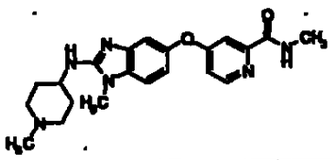
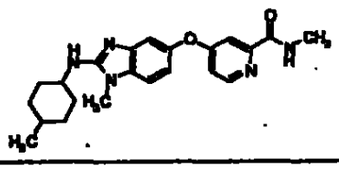
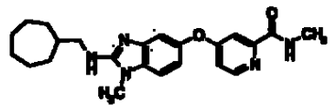
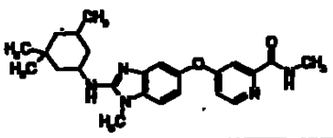
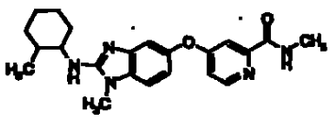
Example	Structure	Name	MH+
325		4-[(2-{[3-(diethylamino)-propyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	411.5
326		4-({2-[(4-bromo-2-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	487.8
327		4-({2-[(3,5-dimethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	402.5
328		4-({2-[(cyclopropylmethyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	352.4
329		4-{[2-(2,3-dihydro-1,4-benzodioxin-6-ylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	432.4
330		N-methyl-4-[(1-methyl-2-{[4-(phenyloxy)pyridin-3-yl]-amino}-1H-benzimidazol-5-yl)-oxy]pyridine-2-carboxamide	467.5
331		N-methyl-4-({1-methyl-2-[(4-pyridin-2-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	451.5
332		4-({2-[(2-chloro-4-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	426.8
333		4-({2-[(4-fluoro-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	406.4

Example	Structure	Name	MH+
334		N-methyl-4-({1-methyl-2-[(2,4,5-trimethylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	416.5
335		4-[(2-{[2-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	476.9
336		4-({2-[(5-chloro-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	422.9
337		4-({2-[(4-chloro-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	426.8
338		N-methyl-4-[(1-methyl-2-{[3-(1-methylpropyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	430.5
339		4-({2-[(4-fluoro-3-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	406.4
340		4-({2-[(4-chloro-3-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	422.9
341		4-{[2-({3-bromo-4-[(trifluoro-methyl)oxy]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	537.3

Example	Structure	Name	MH+
342		4-{[2-({3-chloro-4-[(trifluoro-methyl)oxy]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	492.9
343		N-methyl-4-({1-methyl-2-[(4-pyridin-3-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	451.5
344		4-[(2-{[3-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	476.9
345		4-({2-[(4-chloro-3-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	426.8
346		4-({2-[(2-bromo-4-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	467.3
347		N-methyl-4-({1-methyl-2-[(2,3,5-trifluorophenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	428.4
348		4-({2-[(2,4-dibromophenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	532.2
349		4-({2-[(2-chloro-5-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	426.8
350		4-{[2-({3-chloro-4-[(trifluoro-methyl)thio]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	508.9

Example	Structure	Name	MH+
351		4-({2-[(3-chloro-1H-indol-6-yl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	447.9
352		4-[(2-{[3,5-bis(1,1-dimethylethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	486.6
353		4-[(2-{[5-(1,1-dimethylethyl)-2-(methyloxy)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	460.5
354		N-methyl-4-[(1-methyl-2-{[2-(methyloxy)-5-(1-methyl-1-phenylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	522.6
355		4-[(2-{[4-chloro-2,5-bis(methyloxy)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	468.9
356		4-{[2-({4-fluoro-2-[(1-methylethyl)oxy]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	450.5
357		N-methyl-4-{[1-methyl-2-({3-[(1-methylethyl)oxy]phenyl}-amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	432.5
358 (synthesis as in Ex 769)		4-({2-[(3-furan-3-ylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	440.5

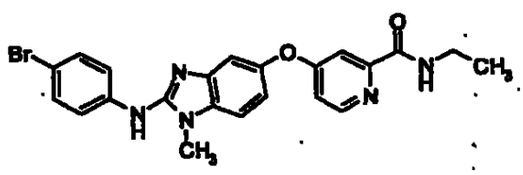
Example	Structure	Name	MH+
359		4-[(2-{[4-chloro-5-methyl-2-(methyloxy)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	452.9
360		N-methyl-4-[(1-methyl-2-{[2-methyl-5-(1-methylethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	430.5
361		4-[(2-{[2,5-bis(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	486.6
362		4-{[2-({5-chloro-2-[(difluoro-methyl)oxy]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	474.9
363		N-methyl-4-{[1-methyl-2-({4-[(phenylmethyl)oxy]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	480.5
364		4-({2-[(2-{[cyclohexyl(methyl)-amino]methyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	499.6
365		N-methyl-4-({1-methyl-2-[(6-pyrrolidin-1-ylpyridin-3-yl)-amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	444.5
366		4-[(2-{[6-(dimethylamino)-pyridin-3-yl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	418.4

Example	Structure	Name	MH+
367		N-methyl-4-({1-methyl-2-[(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	395.4
368		N-methyl-4-({1-methyl-2-[(4-methylcyclohexyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	394.4
369		4-({2-[(cycloheptylmethyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	408.5
370		N-methyl-4-({1-methyl-2-[(3,3,5-trimethylcyclohexyl)-amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	422.5
371		N-methyl-4-({1-methyl-2-[(2-methylcyclohexyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	394.4

Example 372

Synthesis of 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-ethylpyridine-2-carboxamide

The compound 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-ethylpyridine-2-carboxamide was synthesized as follows:



Step 1. Synthesis of *tert*-butyl 4-chloropyridine-2-carboxylate:

4-chloropyridine-2-carbonyl chloride (1eq) was suspended in anhydrous tetrahydrofuran. Then 2 equivalents of a solution of 1 M potassium *tert*-butoxide was added dropwise to the reaction slowly as the reaction was stirring under nitrogen. After 3-4 hours or when the reaction was determined to be complete by HPLC, the reaction was

evaporated under reduced pressure and diluted with ethyl acetate. The organic layer was washed with water followed by brine and dried over anhydrous sodium sulfate. The organic extracts were evaporated under reduced pressure to yield the *tert*-butyl ester as a yellow oil. MS: MH+ = 214.0.

Step 2. Synthesis of *tert*-butyl 4-(4-amino-3-nitrophenoxy)pyridine-2-carboxylate:

Solid anhydrous white powdered KHMDS (2eq) was suspended in a solution of dimethylformamide. Red crystalline 4-amino-3-nitrophenol (1eq) was charged to the rapidly stirring solution under an inert atmosphere and the heterogeneous solution was allowed to stir for 2 hours. Then a dimethylformamide solution of *tert*-butyl 4-chloropyridine-2-carboxylate (1eq) was added dropwise. Anhydrous powdered potassium carbonate (1.2eq) was charged to the reaction as an acid scavenger. The purple colored viscous mixture was heated to 80°C for 12-15 hours until when it was determined to be complete by HPLC. The reaction was evaporated under reduced pressure and diluted with excess ethyl acetate and water. An extraction of the aqueous layer was made with ethyl acetate. The organic layers were combined and washed 4 times with water followed by brine. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude material was purified by flash silica gel chromatography using an eluent of 1:1 mixture of hexanes to ethyl acetate to give the desired product. MS: MH+ = 332.

Step 3. Synthesis of *tert*-butyl 4-[3-nitro-4-(2,2,2-trifluoroacetylamino) phenoxy] pyridine-2-carboxylate:

Trifluoroacetic anhydride (1eq) was slowly added dropwise to a solution of the above amine in anhydrous methylene chloride under nitrogen. After 10-15 minutes or until the reaction was complete as determined by HPLC, the reaction was quenched with excess saturated aqueous sodium bicarbonate. The product was extracted with methylene chloride from the aqueous layer and washed with water and brine. The extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the title product as a yellow solid. MS: $MH^+ = 428$.

Step 4. Synthesis of tert-butyl 4-[3-nitro-4-(2,2,2-trifluoro-*N*-methylacetylamino) phenoxy] pyridine-2-carboxylate:

A solution of *tert*-butyl 4-[3-nitro-4-(2,2,2-trifluoroacetylamino) phenoxy] pyridine-2-carboxylate (1eq) and sodium carbonate (4eq) in dimethylformamide was

stirred at 20°C under nitrogen for thirty minutes before 2 equivalents of iodomethane (2eq) was charged slowly dropwise to the reaction. After 2-3 hours or until it was determined to be complete by HPLC, the reaction was evaporated under reduced pressure. The crude mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the title product as an orange solid. MS: $MH^+ = 442$.

Step 5. Synthesis of *tert*-butyl 4-[4-(methylamino)-3-nitrophenoxy]pyridine-2-carboxylate:

A solution of tert-butyl 4-[3-nitro-4-(2,2,2-trifluoro-*N*-methylacetylamino) phenoxy] pyridine-2-carboxylate in ethanol was stirred at room temperature. 1N sodium hydroxide was slowly dropped into the reaction until the conversion was complete by HPLC. The reaction was evaporated under reduced conditions and then extracted with ethyl acetate and washed with a saturated aqueous solution of ammonium chloride followed by water and brine. The organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the product as an orange solid. MS: $MH^+ = 346$

Step 6. Synthesis of *tert*-butyl 4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate:

A solution of *tert*-butyl 4-[4-(methylamino)-3-nitrophenoxy]pyridine-2-carboxylate (1eq) and 10% palladium on carbon (0.1eq) in methanol was stirred at room temperature and flushed with nitrogen. Hydrogen was flushed through the reaction for 1-2 hours or until the reaction was determined to be complete by HPLC. Nitrogen was flushed through the reaction for 15 minutes before the reaction was filtered through a celite pad. The celite pad was washed with excess methanol followed by concentration under reduced pressure to afford the product as a light yellow solid. MS: $MH^+ = 316$.

Step 7. Synthesis of *tert*-butyl 4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}pyridine-2-carboxylate:

A solution of the diamine from step 6 (1eq) and 4-bromophenyl isothiocyanate (1eq) in anhydrous tetrahydrofuran under nitrogen was stirred at 20°C for 2-3 hours or when determined to be complete by HPLC. The solution was treated with 3 equivalents of 1-ethyl-(3-dimethylaminopropyl) carbodiimide HCl. The stirred solution was heated to 50°C under nitrogen for 2-3 hrs or until the reaction is determined to be complete by HPLC. The reaction was evaporated under reduced pressure and then diluted with ethyl

acetate and water. The aqueous layer was back extracted with ethyl acetate. The combined organic layers were washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and later evaporated under reduced pressure. The crude material was purified by reverse high-pressure liquid chromatography to afford the product as a brown powder after lyophlization. MS: MH^+= 495.

Step 8. Synthesis of 4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yl-oxy}pyridine-2-carboxylic acid

A solution of the product of step 7 in trifluoroacetic acid was treated with two drops of water at room temperature for 3-4 hours or until the reaction was determined to be complete by HPLC. The reaction was evaporated under reduced pressure to afford the product as a red-orange oil in quantitative yield. MS: MH^+ = 439.

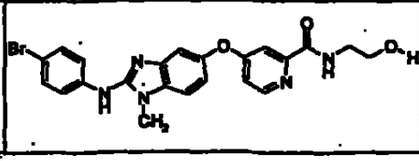
Step 9. Synthesis of 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-ethylpyridine-2-carboxamide:

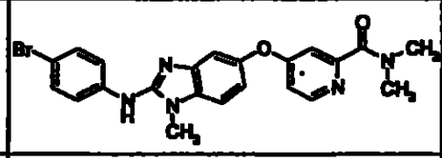
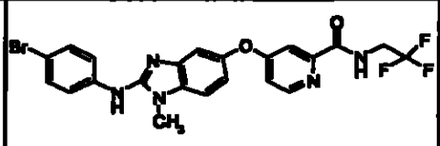
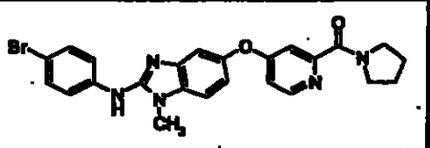
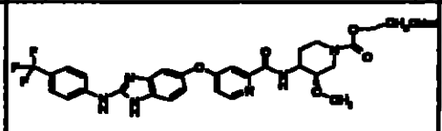
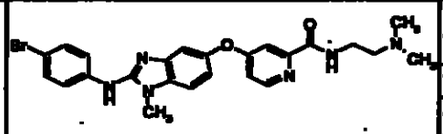
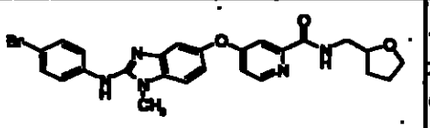
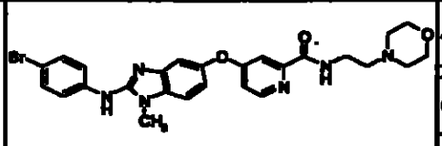
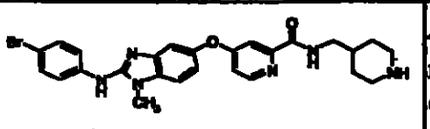
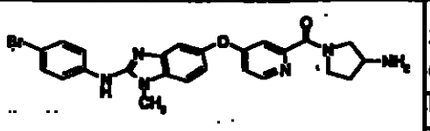
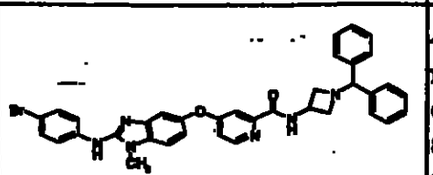
A solution of above (1eq) in anhydrous tetrahydrofuran (0.5 ml) was treated with *O*-benzotriazol-1-yl N,N,N',N'-tetramethyl uronium hexafluorophosphate (2eq), excess diisopropylethyl amine, and ethyl amine (1eq). The reaction was left stirring under nitrogen for 12-15 hours. The reaction was evaporated under reduced pressure and diluted with ethyl acetate. The ethyl acetate layer was washed once with water and then evaporated under reduced pressure. The crude material was purified by reverse high-pressure liquid chromatography and recovered as TFA salt after lyophilization. MS: MH^+= 466.

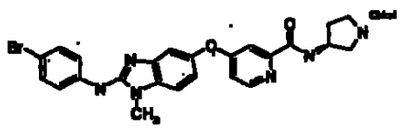
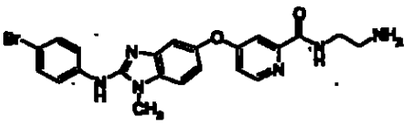
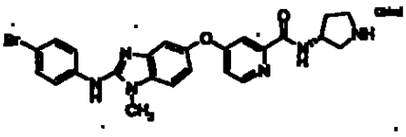
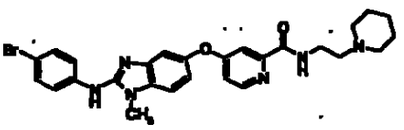
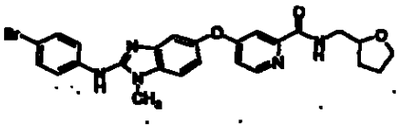
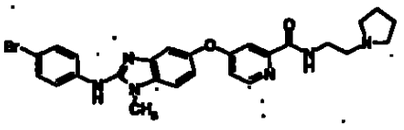
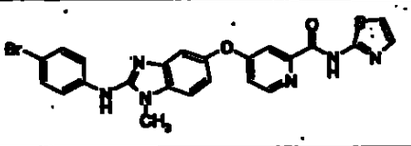
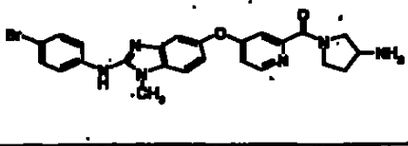
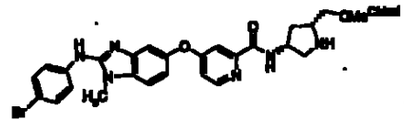
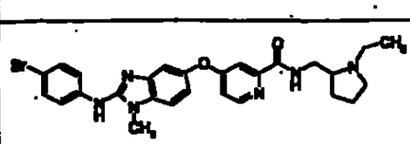
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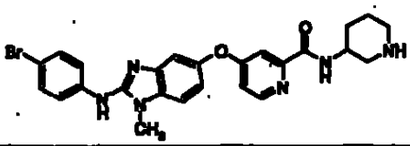
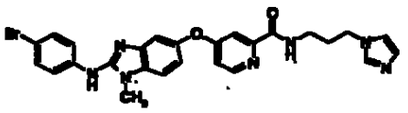
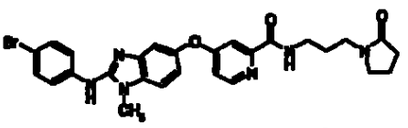
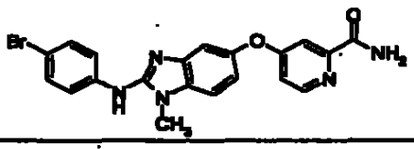
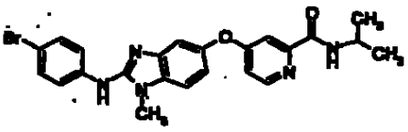
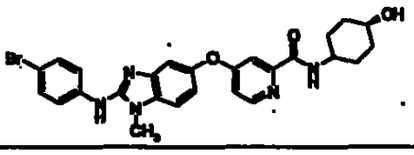
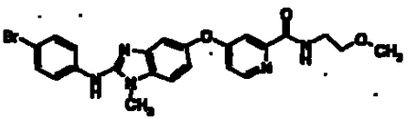
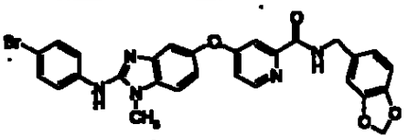
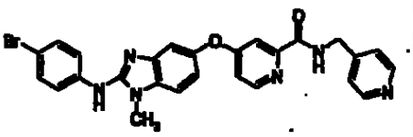
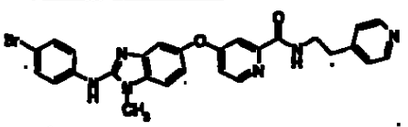
The compounds shown in the following Table 4 (Examples 373-447) were prepared from following the procedure described for Example 372.

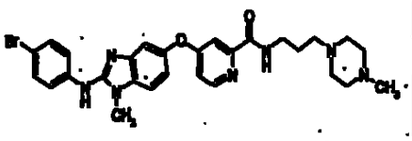
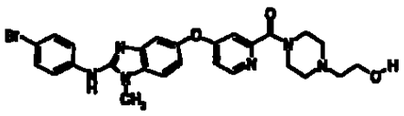
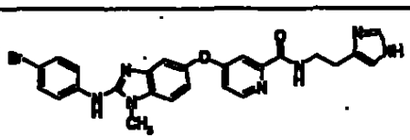
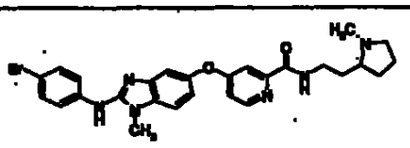
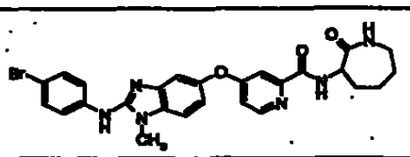
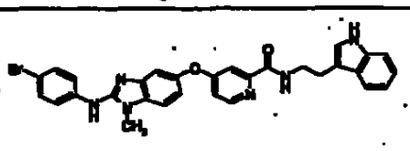
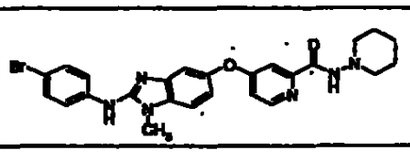
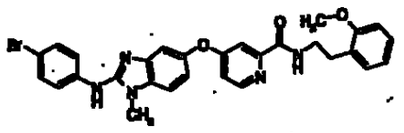
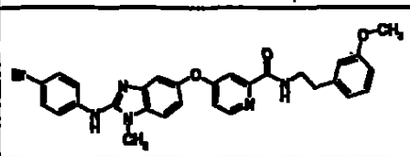
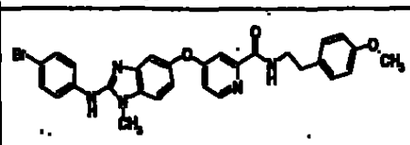
Table 4

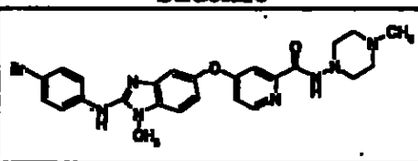
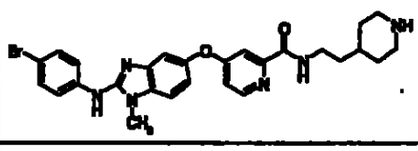
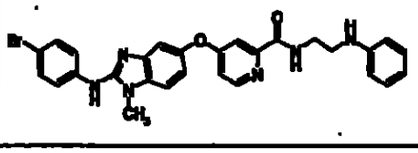
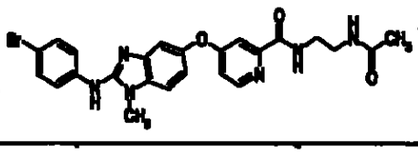
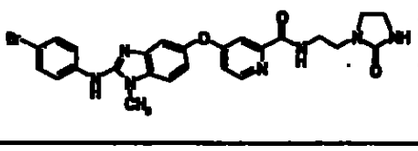
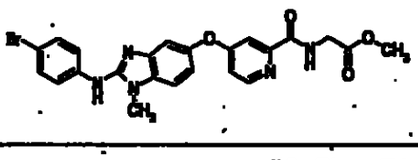
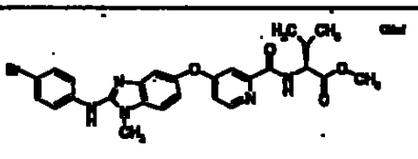
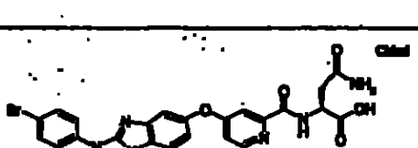
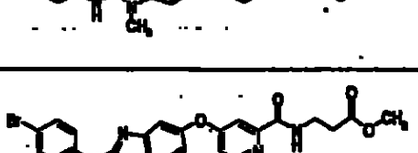
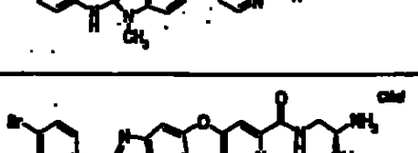
Example	Structure	Name	MH+
373		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	482

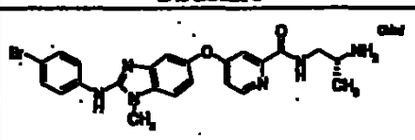
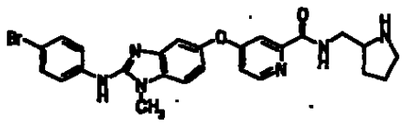
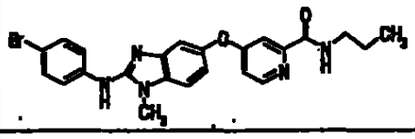
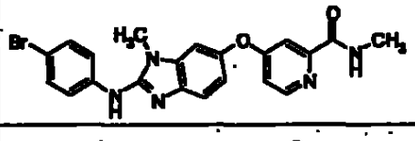
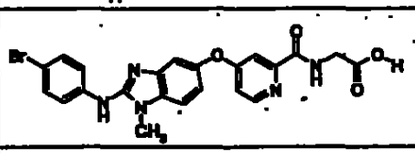
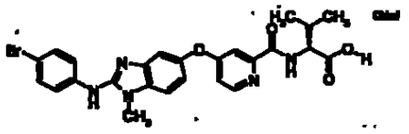
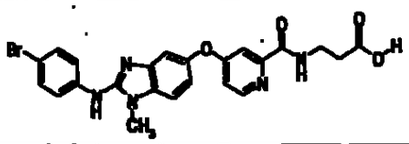
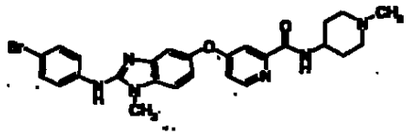
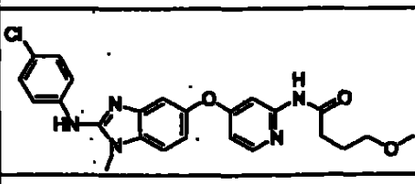
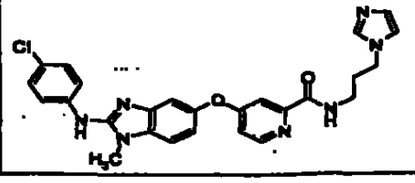
Example	Structure	Name	MH+
374		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N,N-dimethylpyridine-2-carboxamide	466
375		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-(2,2,2-trifluoroethyl)-pyridine-2-carboxamide	521
376		N-(4-bromophenyl)-1-methyl-5-{[2-(pyrrolidin-1-ylcarbonyl)-pyridin-4-yl]oxy}-1H-benzimidazol-2-amine	492
377		ethyl (3R)-3-(methyloxy)-4-[({4-[(2-{[4-(trifluoromethyl)phenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}carbonyl)-amino]piperidine-1-carboxylate	599
378		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(dimethylamino)-ethyl]pyridine-2-carboxamide	509
379		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-(tetrahydrofuran-2-yl-methyl)pyridine-2-carboxamide	522
380		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-(2-morpholin-4-ylethyl)-pyridine-2-carboxamide	551
381		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-(piperidin-4-ylmethyl)-pyridine-2-carboxamide	535
382		5-({2-[(3-aminopyrrolidin-1-yl)-carbonyl]pyridin-4-yl}oxy)-N-(4-bromophenyl)-1-methyl-1H-benzimidazol-2-amine	507
383		4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-[1-(diphenylmethyl)-azetidin-3-yl]pyridine-2-carboxamide	659

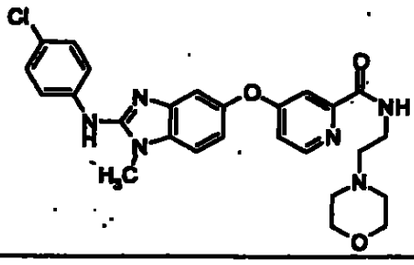
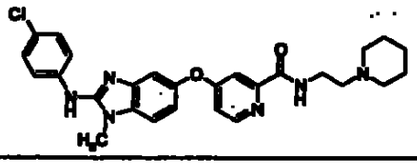
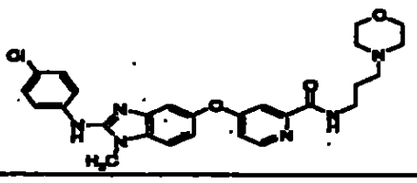
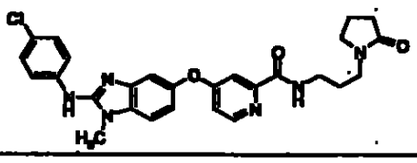
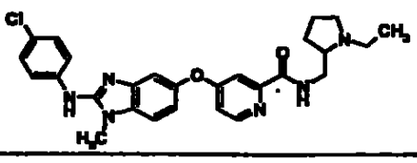
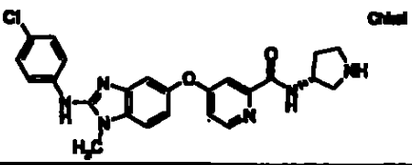
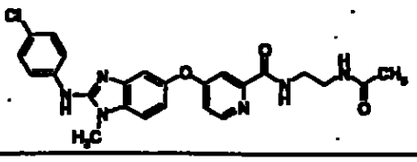
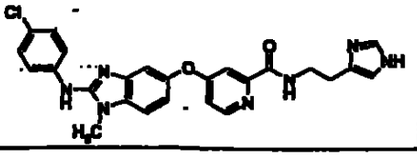
Example	Structure	Name	MH+
384		N-((3S)pyrrolidin-3-yl)(4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	507.0
385		N-(2-aminoethyl)(4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	481.0
386		N-((3R)pyrrolidin-3-yl)(4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	507.0
387		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-piperidylethyl)-carboxamide	549.1
388		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(oxolan-2-ylmethyl)-carboxamide	522.0
389		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-pyrrolidinylethyl)-carboxamide	535.1
390		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(1,3-thiazol-2-yl)-carboxamide	521.0
391		3-aminopyrrolidinyl 4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl) ketone	507.0
392		N-[(3R,5R)-5-(methoxymethyl)-pyrrolidin-3-yl](4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	551.1
393		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[(1-ethylpyrrolidin-2-yl)methyl]carboxamide	549.2

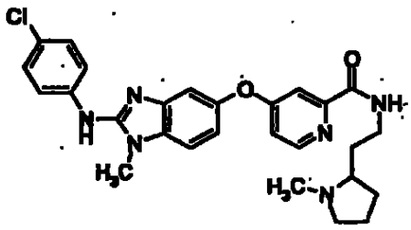
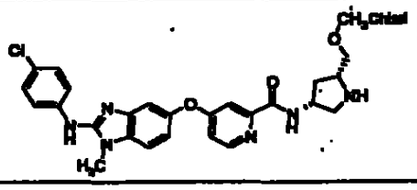
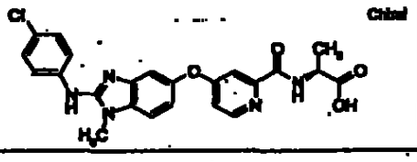
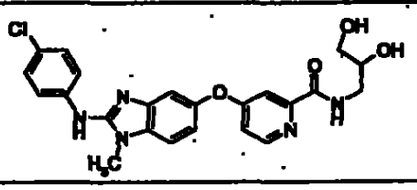
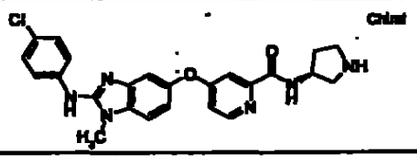
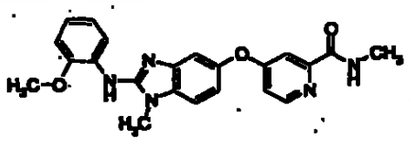
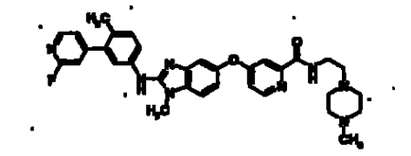
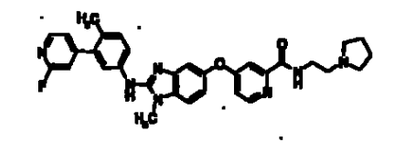
Example	Structure	Name	MH+
394		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(3-piperidyl)-carboxamide	521.0
395		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(3-imidazolylpropyl)-carboxamide	546.4
396		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[3-(2-oxo-pyrrolidinyl)propyl]carboxamide	563.4
397		4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}-pyridine-2-carboxamide	438.1
398		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(methylethyl)-carboxamide	480.3
399		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(4-hydroxy-cyclohexyl)carboxamide	536.4
400		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-methoxyethyl)-carboxamide	496.3
401		N-(2 h-benzo[d]1,3-dioxolen-5-ylmethyl)(4-{2-[(4-bromophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))carboxamide	572.4
402		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(4-pyridylmethyl)-carboxamide	529.3
403		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-(4-pyridyl)ethyl)-carboxamide	543.4

Example	Structure	Name	MH+
404		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[3-(4-methyl-piperazinyl)propyl]carboxamide	578.5
405		4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl) 4-(2-oxyethyl)piperazinyl ketone	551.4
406		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-imidazol-4-ylethyl)carboxamide	532.4
407		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]carboxamide	549.1
408		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-oxoazaperhydro-epin-3-yl)carboxamide	549.1
409		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-indol-3-ylethyl)-carboxamide	581.4
410		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-piperidylcarboxamide	521.1
411		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[2-(2-methoxyphenyl)-ethyl]carboxamide	572.1
412		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[2-(3-methoxyphenyl)-ethyl]carboxamide	572.4
413		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[2-(4-methoxyphenyl)-ethyl]carboxamide	572.4

Example	Structure	Name	MH+
414		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(4-methylpiperazinyl)-carboxamide	536.1
415		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-(4-piperidyl)ethyl)-carboxamide	549.4
416		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[2-(phenylamino)-ethyl]carboxamide	557.4
417		N-{2-[(4-{2-[(4-bromophenyl)-amino]-1-methylbenzimidazol-5-yloxy}-2-pyridyl)carbonylamino]-ethyl}acetamide	523.4
418		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[2-(2-oxo-imidazolidinyl)ethyl]carboxamide	550.4
419		methyl 2-[(4-{2-[(4-bromophenyl)-amino]-1-methylbenzimidazol-5-yloxy}-2-pyridyl)carbonylamino]-acetate	510.3
420		methyl (2S)-2-[(4-{2-[(4-bromo-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carbonylamino]-3-methylbutanoate	552.4
421		(2S)-2-[(4-{2-[(4-bromo-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carbonylamino]-3-carbamoylpropanoic acid	553.3
422		methyl 3-[(4-{2-[(4-bromo-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}-2-pyridyl)-carbonylamino]propanoate	524.3
423		N-((2S)-2-aminopropyl)(4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	495.3

Example	Structure	Name	MH+
424		N-((2R)-2-aminopropyl)(4-{2-[(4-bromophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	495.3
425		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(pyrrolidin-2-yl-methyl)carboxamide	521.4
426		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-propylcarboxamide	480.3
427		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-6-yloxy}(2-pyridyl))-N-methylcarboxamide	452.1
428		2-[(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}-2-pyridyl)carbonylamino]acetic acid	496.31
429		(2S)-2-[(4-{2-[(4-bromophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))carbonylamino]-3-methylbutanoic acid	538.1
430		3-[(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}-2-pyridyl)carbonylamino]propanoic acid	510.1
431		(4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(1-methyl(4-piperidyl))carboxamide	535.1
432		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(3-methoxypropyl)-carboxamide	466.1
433		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(3-imidazolylpropyl)-carboxamide	502.1

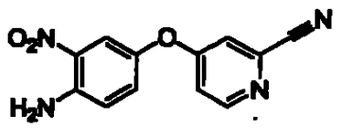
Example	Structure	Name	MH+
434		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-morpholin-4-yl-ethyl)carboxamide	507.2
435		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-piperidylethyl)-carboxamide	505.2
436		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(3-morpholin-4-yl-propyl)carboxamide	521.2
437		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[3-(2-oxo-pyrrolidinyl)propyl]carboxamide	519.2
438		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[(1-ethylpyrrolidin-2-yl)methyl]carboxamide	505.2
439		N-((3R)pyrrolidin-3-yl)(4-{2-[(4-chlorophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	463.2
440		N-{2-[(4-{2-[(4-chlorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}-2-pyridyl)carbonylamino]-ethyl}acetamide	479.2
441		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-(2-imidazol-4-yl-ethyl)carboxamide	488.2

Example	Structure	Name	MH+
442		(4-{2-[(4-chlorophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]carboxamide	505.2
443		N-[(3R,5R)-5-(methoxymethyl)-pyrrolidin-3-yl](4-{2-[(4-chloro-phenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	507.2
444		(2S)-2-[(4-{2-[(4-chlorophenyl)-amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))carbonylamino]-propanoic acid	466.1
445		N-(2,3-dihydroxypropyl)(4-{2-[(4-chlorophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	468.1
446		N-((3S)pyrrolidin-3-yl)(4-{2-[(4-chlorophenyl)amino]-1-methyl-benzimidazol-5-yloxy}(2-pyridyl))carboxamide	463.2
447 (synthesis as in Ex 120a)		(4-{2-[(2-methoxyphenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide	404.1
448 (synthesis as in Ex 483)		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(4-methylpiperazin-1-yl)ethyl]-pyridine-2-carboxamide	595.7
448 (synthesis as in Ex 483)		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyrrolidin-1-ylethyl)pyridine-2-carboxamide	566.7

Example 450

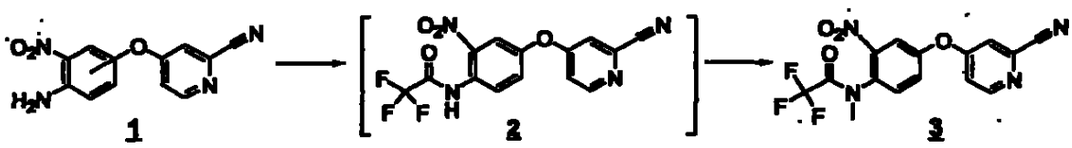
Preparation of (4-Chloro-phenyl)-{5-[2-(4,5-dihydro-1H-imidazol-2-yl)-pyridin-4-yloxyl-1-methyl-1H-benzoimidazol-2-yl}-amine)

Step 1. Synthesis of 4-(4-Amino-3-nitro-phenoxy)-pyridine-2-carbonitrile:



Potassium carbonate (9.00g) was dried *in vacuo* with heating, cooled to RT under nitrogen. 4-amino-3-ntrophenol (3.355 g), 4-chloro-2-cyanopyridine (3.00 g) and DMSAO (30 mL, anhydrous) were added. The system was stirred under nitrogen as it was heated to 103°C, and held at this temperature 1 hr. The reaction was then cooled to RT, poured onto ice/H_2O (500 mL) the precipitate was collected, washed (H_2O), dissolved (EtOAc), dried (Na_2SO_4), filtered and stripped to a solid. This was suspended (Et_2O), collected, air-dried 4.1015 g (73.5%) a second crop was collected (0.5467 gm, 10%). M/z=257 (M+1)

Step 2. Synthesis of N-[4-(2-Cyano-pyridin-4-yloxy)-2-nitro-phenyl]-2,2,2-trifluoro-N-methyl-acetamide:

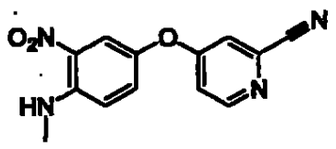


Potassium carbonate (1.6g) was dried *in vacuo* with heating, cooled to RT and suspended in dichloromethane (30 mL) with 4-(4-amino-3-nitro-phenoxy)-pyridine-2-carbonitrile (2.005 gm) under nitrogen. This was cooled to 0°C and TFAA (2.2mL) was added, neat. The starting material goes into solution rapidly as addition is made. After 10 min at 0°C, the mixture was diluted with dichloromethane, washed (H_2O, aq NaCl), dried (K_2CO_3), filtered and stripped to a yellow foam. M/z=353 (M+1) The product was used without purification.

Iodomethane (0.53 mL) was added to a suspension of potassium carbonate (1.858 g) in DMF (30 mL containing compound 2 (~7.8 mmole) under nitrogen. The

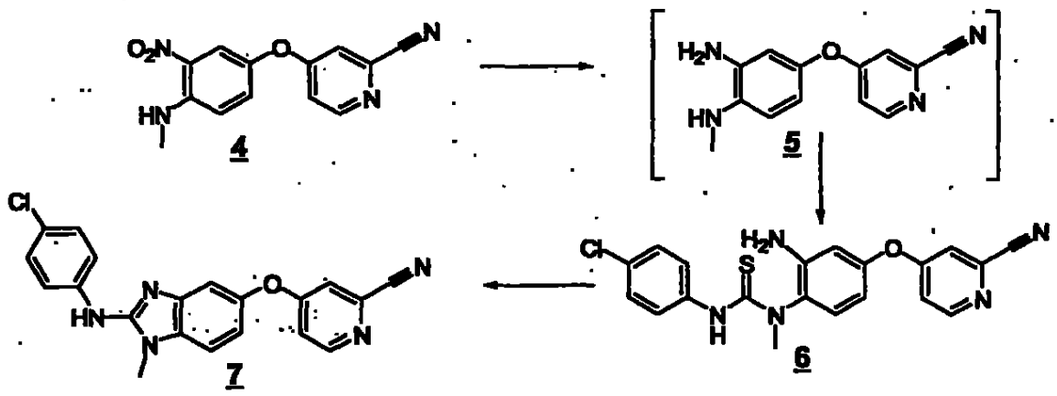
suspension stirred at RT overnight, then poured onto H_2O (300 mL), extracted (Et_2O, 3x 150 mL), the combined extracts were washed (H_2O, aq. NaCl), dried (potassium carbonate), filtered and stripped to an orange oil (7.4922 g). M/z=367 (M+1)

Step 3. Synthesis of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carbonitrile:



NaOH (1 mL, 1N aq) was added dropwise to a solution of N-[4-(2-cyano-pyridin-4-yloxy)-2-nitro-phenyl]-2,2,2-trifluoro-N-methyl-acetamide (440 mg) in ethanol (6 mL) at RT. After 40 min, the mixture was diluted with H_2O (20 mL) and cooled to 0°C. Bright orange crystals were collected, washed (H2O) and air-dried 311.1 mg (94%). M/z=271 (M+1).

Step 4. Synthesis of 4-[2-(4-Chloro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carbonitrile:



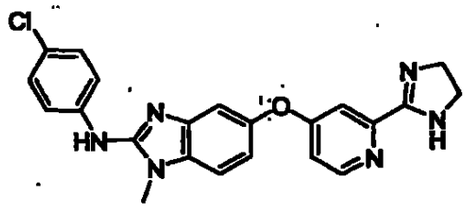
Palladium on carbon (46 mg 10% w/w) was suspended in MeOH (2 mL) under nitrogen. The resulting suspension was added, under nitrogen, to a suspension of 4-(4-methylamino-3-nitro-phenoxy)-pyridine-2-carbonitrile (311 mg) in MeOH (3mL) at RT. The atmosphere was exchanged with hydrogen, and the system stirred vigorously under 1 atm hydrogen for 1 hr. The atmosphere was then exchanged for nitrogen, the mixture was filtered (celite) and the filtrate was used without further purification in the next reaction. M/z=2421 (M+1).

4-chlorophenylisothiocyanate (200 mg) was added to a solution of compound 5 in MeOH (10 mL). The solution was stirred at reflux for 2 hrs. Iodomethane (71 microliters) was added, and stirring continued at 67°C, overnight. The mixture was then cooled to RT evaporated to dryness, and the residue chromatographed (0.5% NH_4OH, 5% MeOH, 94.5% dichloromethane on silica gel) to isolate a compound of Rf=0.29 (325 mg). This was crystallized from dichloromethane/ether to give 127 mg. M/z=376 (M+1)

1HNMR (MeOH-d4)

9.40ppm	s(b)		(1H)
8.55ppm	d,d	H=5.7, 0.6Hz	(1H)
7.62ppm	m		(2 h)
7.42 ppm	d,d	J=2.5, 0.6Hz	(1H)
7.43 ppm	d		(1H)
7.37 ppm	m		(2 h)
7.21 ppm	d	J=2.0Hz	(1H)
7.15 ppm	d,d	J=5.9, 2.5Hz	(1H)
6.97 ppm	d,d	J=8.4,2.2 hz	(1H)
3.80 ppm	s		(3H)

Step 5. Synthesis of (4-Chloro-phenyl)-{5-[2-(4,5-dihydro-1H-imidazol-2-yl)-pyridin-4-yloxy]-1-methyl-1H-benzoimidazol-2-yl}-amine:



H_2SO_4 (454 mg) was added cautiously to a suspension of 4-[2-(4-chloro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carbonitrile (60.0 mg) in ethylenediamine (0.50 mL). The system was shaken at room temperature for 72 hrs, then poured onto ice/$NaHCO_3$. The solid product was collected, washed (H_2O) air-dried 59.8 mg. M/z=419 (M+1).

Example 451

Synthesis of (4-{2-[(4-bromophenyl)amino]benzoxazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide

Step 1. Synthesis of 2-amino-4-methoxyphenol

The mixture containing 4-methoxy-2-nitrophenol in methanol with catalytic amount of 10%Pd/C was hydrogenated until disappearance of yellow color to yield 2-amino-4-methoxyphenol. MS: MH+ = 140.

Step 2. Synthesis of 5-methoxybenzoxazole-2-thiol

The mixture containing 2-amino-4-methoxyphenol(1eq) and O-ethylxanthic acid, potassium salt (1.1eq) in pyridine was refluxed for two hours. The resultant mixture was poured in to ice/water containing hydrochloric acid to yield a 5-methoxybenzoxazole-2-thiol as a tan solid. MS: MH+ = 182

Step 3. Synthesis of 2-chloro-5-methoxybenzoxazole

The mixture containing 5-methoxybenzoxazole-2-thiol was heated in thionyl chloride with a drop of DMF. The resultant mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried and concentrated. Purification on a silica gel column gave 2-chloro-5-methoxybenzoxazole as a white solid. MS: MH+ = 184.

Step 4. Synthesis of (4-bromophenyl)(5-methoxybenzoxazol-2-yl)amine

The mixture containing 2-chloro-5-methoxybenzoxazole(1eq), 4-bromoaniline (2eq) and diisopropylethylamine was refluxed in dimethylformamide. The resultant mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried. Purification on silica gel gave (4-bromophenyl)(5-methoxybenzoxazol-2-yl)amine. MS: MH+ = 318

Step 5. Synthesis of 2-[(4-bromophenyl)amino]benzoxazol-5-ol

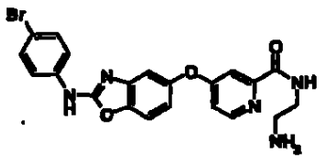
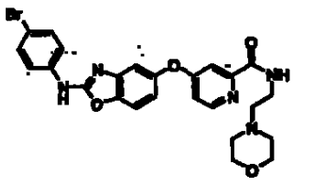
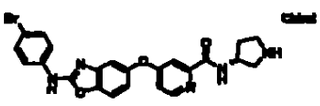
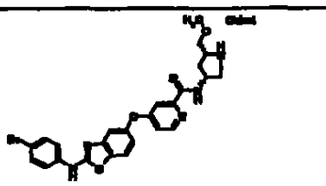
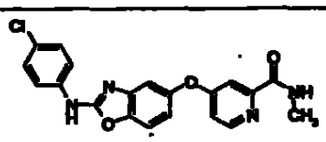
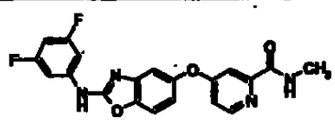
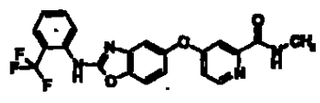
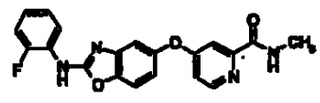
The mixture of (4-bromophenyl)(5-methoxybenzoxazol-2-yl)amine and hydrobromic acid (48%) was subjected to the microwave at 150°C for 6mins to yield 2-[(4-bromophenyl)amino]benzoxazol-5-ol. MS: MH+ = 305

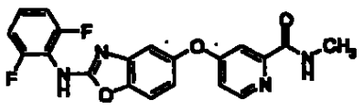
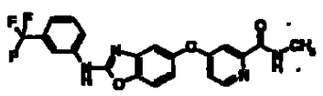
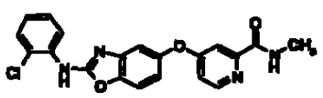
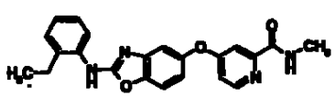
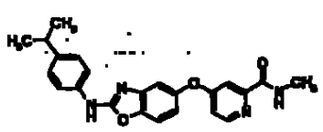
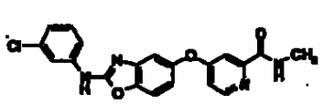
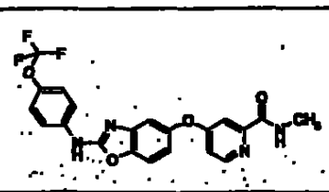
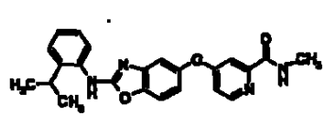
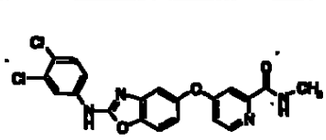
Step 6. Synthesis of (4-{2-[(4-bromophenyl)amino]benzoxazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide

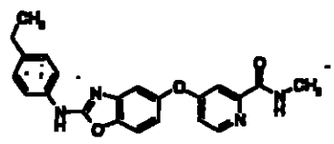
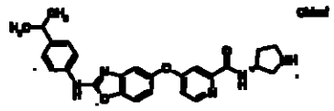
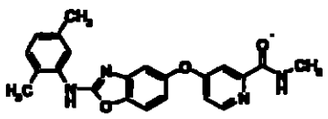
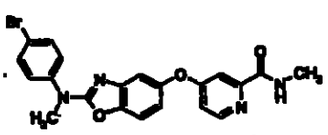
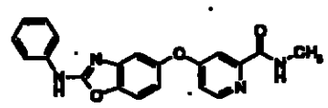
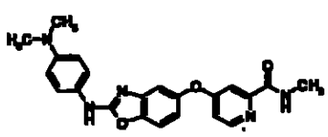
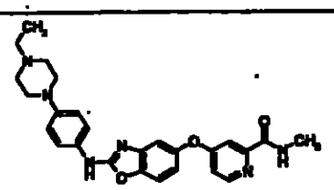
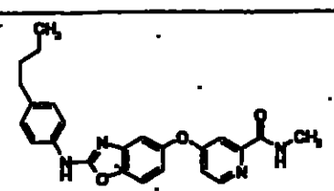
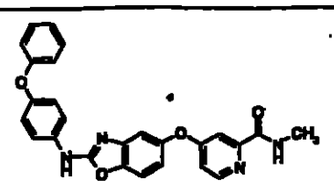
The mixture containing 2-[(4-bromophenyl)amino]benzoxazol-5-ol (1eq), potassium bis(trimethylsilyl)amide (4eq), was stirred in dimethylformamide for 30 min at room temperature. To this mixture was added (4-chloro(2-pyridyl)-N-methyl-carboxamide (1eq) and Potassium carbonate (1.2eq) and microwaved for 6 mins at 150°C. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried, filtered and concentrated. Purification on Prep LC yielded the desired product. MS: MH+ = 439.

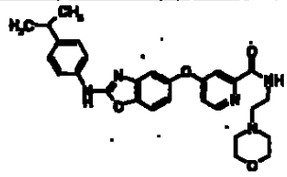
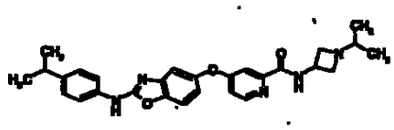
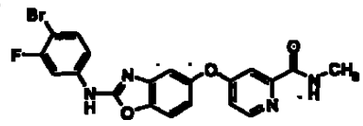
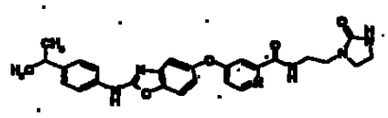
The compounds shown in the following Table 5 (Examples 452-481) were prepared from following the procedure described for Examples 449-451.

Table 5

Example	Structure	Name	MH+
452		N-(2-aminoethyl)-4-({2-[(4-bromophenyl)amino]-1,3-benzoxazol-5-yl}oxy)pyridine-2-carboxamide	469.3
453		4-({2-[(4-bromophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	539.4
454		4-({2-[(4-bromophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-[(3R)-pyrrolidin-3-yl]pyridine-2-carboxamide	495.3
455		4-({2-[(4-bromophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-{(3R,5R)-5-[(methyloxy)methyl]pyrrolidin-3-yl}pyridine-2-carboxamide	539.4
456		4-({2-[(4-chlorophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	395.8
457		4-({2-[(3,5-difluorophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	397.4
458		N-methyl-4-[(2-{[2-(trifluoromethyl)phenyl]amino}-1,3-benzoxazol-5-yl)oxy]pyridine-2-carboxamide	429.4
459		4-({2-[(2-fluorophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	379.4

Example	Structure	Name	MH+
460		4-({2-[(2,6-difluorophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	397.4
461		N-methyl-4-[(2-{[3-(trifluoromethyl)phenyl]amino}-1,3-benzoxazol-5-yl)oxy]pyridine-2-carboxamide	429.4
462		4-({2-[(2-chlorophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	395.8
463		4-({2-[(2-ethylphenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	389.4
464		N-methyl-4-[(2-{[4-(1-methylethyl)phenyl]amino}-1,3-benzoxazol-5-yl)oxy]pyridine-2-carboxamide	403.5
465		4-({2-[(3-chlorophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	395.8
466		N-methyl-4-{[2-({4-[(trifluoromethyl)oxy]phenyl}amino)-1,3-benzoxazol-5-yl]oxy}pyridine-2-carboxamide	445.4
467		N-methyl-4-[(2-{[2-(1-methylethyl)phenyl]amino}-1,3-benzoxazol-5-yl)oxy]pyridine-2-carboxamide	403.5
468		4-({2-[(3,4-dichlorophenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	430.3

Example	Structure	Name	MH+
469		4-({2-[(4-ethylphenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	389.4
470		4-[(2-{[4-(1-methylethyl)phenyl]amino}-1,3-benzoxazol-5-yl)oxy]-N-[(3R)-pyrrolidin-3-yl]pyridine-2-carboxamide	458.5
471		4-({2-[(2,5-dimethylphenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	389.4
472		4-({2-[(4-bromophenyl)(methyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	454.3
473		N-methyl-4-{[2-(phenylamino)-1,3-benzoxazol-5-yl]oxy}pyridine-2-carboxamide	361.4
474		4-[(2-{[4-(dimethylamino)phenyl]amino}-1,3-benzoxazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	404.4
475		4-[(2-{[4-(4-ethylpiperazin-1-yl)-phenyl]amino}-1,3-benzoxazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	473.5
476		4-({2-[(4-butylphenyl)amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	417.5
477		N-methyl-4-[(2-{[4-(phenyloxy)-phenyl]amino}-1,3-benzoxazol-5-yl)oxy]pyridine-2-carboxamide	453.5

Example	Structure	Name	MH+
478		4-[(2-{[4-(1-methylethyl)phenyl]-amino}-1,3-benzoxazol-5-yl)oxy]-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	502.6
479		N-[1-(1-methylethyl)azetidin-3-yl]-4-[(2-{[4-(1-methylethyl)phenyl]-amino}-1,3-benzoxazol-5-yl)oxy]-pyridine-2-carboxamide	486.6
480		4-({2-[(4-bromo-3-fluorophenyl)-amino]-1,3-benzoxazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	458.3
481		4-[(2-{[4-(1-methylethyl)phenyl]-amino}-1,3-benzoxazol-5-yl)oxy]-N-[2-(2-oxoimidazolidin-1-yl)-ethyl]pyridine-2-carboxamide	501.6

Example 482

Synthesis of [4-(2-{[4-(dimethylamino)phenyl]amino –1-methyl benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

Step 1. Synthesis of 4-(2-{[4-(dimethylamino)phenylamino)-1-methyl-benzimidazol-5-yloxy)pyridinr-2-carboxylic acid

To tert-butyl4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 4-(dimethylamino)benzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. The mixture was then concentrated and to it was added tetrahydrofuran and 1-ethyl-(3-dimethylaminopropyl)carbodimidehydrochloride (2eq) and stir at ambient temperature for 16 h. tert-butyl4-(2-{[4-dimethylamino)phenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylate crashes out of the reaction mixture. To it in methylene chloride was added trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-dimethylamino)phenylamino)-1-methylbenzimidazol-5-yloxy)-pyridine-2-carboxylic acid was purified by preparative chromatography. MS: MH^+ = 403.

Step 2. Synthesis of [4-(2-{[4-(dimethylamino)phenylamino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide:

To 4-(2-{[4-(dimethylamino)pheylamino)-1-methylbenzimidazol-5-yloxy)-pyridine-2-carboxylic acid (1eq) in tetrahydrofuran was added 2-pyrrolidinylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[4-(dimethylamino)phenyl]amino –1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide. MS: $MH^+ = 498$.

Example 483

Synthesis of [4-(2-{[4-bromo-3-methylphenyl)amino-1-methyl benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

Step 1. Synthesis of 4-{2-[(4-bromo-3-methylphenyl)amino]-1-methyl-benzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 4-bromo-3-methylbenzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-butyl4-(2-{[4-bromo-3-methylphenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-bromo-3-methylphenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: $MH^+ = 452$

Step 2. Synthesis of [4-(2-{[4-bromo-3-methylphenyl)amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

To 4-(2-{[4-bromo-3-methylpheylamino)-1-methylbenzimidazol-5-yloxy)-pyridine-2-carboxylic acid(1eq) in tetrahydrofuran was added 2-pyrrolidinylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[4bromo-3-methylphenyl]amino –1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide. MS: $MH^+ = 549$.

Example 484

Synthesis of [4-(2-{[2-fluro-5-(trifluromethyl)phenyl]amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

Step 1. Synthesis of 4-{2-[(2-fluro-5-(trifluromethyl)phenyl)amino]-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 2-fluro-5-(trifluromethyl)benzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-butyl4-(2-{[2-fluro-5-(trifluromethyl)phenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[2-fluro-5-(trifluromethyl)phenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: $MH^+ = 446$.

Step 2. Synthesis of [4-(2-{[2-fluro-5-(trifluromethyl)phenyl)amino-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide:

To 4-(2-{[2-fluro-5-(trifluromethyl)phenylamino)-1-methylbenzimidazol-5-yl-oxy)pyridine-2-carboxylic acid (1eq) in tetrahydrofuran was added. 2-pyrrolidinyl-ethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[2-fluro-5-(trifluromethyl)phenyl]amino–1-methylbenzimidazol-5-yloxy)-(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide. MS: $MH^+ = 542$.

Example 485

Synthesis of [4-(2-{[4-bromo-3-flurophenyl)amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)carboxamide

Step 1. Synthesis of 4-{2-[(4-bromo-3-flurophenyl)amino]-1-methyl-benzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 4-bromo-3-flurobenzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-

butyl4-(2-{[4-bromo-3-flurophenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-bromo-3-flurophenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: MH^+ = 456.

Step 2. Synthesis of [4-(2-{[4-bromo-3-flurophenyl)amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)carboxamide:

To 4-(2-{[4-bromo-3-flurophenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid (1eq) in tetrahydrofuran was added 2-piperidylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[4-bromo-3-flurophenyl]amino--1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)-carboxamide. MS: MH^+ = 567.

Example 486

Synthesis of 4-{1-methyl-2-[(4-methylphenyl)amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N- (2-pyrrolidinylethyl)carboxamide

Step 1. Synthesis of 4-{1-methyl-2-[(4-methylphenyl)amino]benzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl-4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 4-methylbenzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-butyl-4-{1-methyl-2-[(4-methylphenyl)amino)benzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluro-acetic acid and stirred at ambient temperature overnight. Resulting 4-{1-methyl-2-[(4-methylphenyl)amino]benzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: MH^+ = 374.

Step 2. Synthesis of 4-{1-methyl-2-[(4-methylphenyl)amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N- (2-pyrrolidinylethyl)carboxamide

To 4-{1-methyl-2-[(4-methylphenyl)amino]benzimidazol-5-yloxy)pyridine-2-carboxylic acid (1eq) in tetrahydrofuran was added 2-pyrrolidinylethylamine (2eq),

HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded 4-{1-methyl-2-[(4-methylphenyl)amino-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-2(2-pyrrolidinylethyl)carboxamide. MS: $MH^+ = 470$.

Example 487

Synthesis of [4-(2-{[4-ethylphenyl)amino-1-methyl benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

Step 1. Synthesis of 4-{2-[(4-ethylphenyl)amino]-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 4-ethylbenzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-butyl4-(2-{[4-ethylphenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-ethylphenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: $MH^+ = 388$.

Step 2. Synthesis of [4-(2-{[4-ethylphenyl)amino-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

To 4-(2-{[4-ethylpheylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid (1eq) in tetrahydrofuran was added 2-pyrrolidinylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[4-ethylphenyl]amino--1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinyl-ethyl)carboxamide. MS: $MH^+ = 484$.

Example 488

Synthesis of [4-(2-{[3-(tert-butyl)phenyl]amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)carboxamide

Step 1. Synthesis of 4-{2-[(3-(tert-butyl)phenyl)amino]-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 3-(tert-butyl)benzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-butyl4-(2-{[3-(tert-butyl)phenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluroacetic acid and stirred af ambient temperature overnight. Resulting 4-(2-{[3-(tert-butyl)phenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: MH^+ = 416.

Step 2. Synthesis of [4-(2-{[3-(tert-butyl)phenyl)amino-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)carboxamide

To 4-(2-{[3-(tert-butyl)phenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid (1eq) in tetrahydrofuran was added 2-piperidylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[3-(tert-butyl)phenyl]amino--1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)-carboxamide. MS: MH^+ = 512.

Example 489

Synthesis of [4-(2-{[4-chloro-3-(trifluromethyl)phenyl]amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)carboxamide

Step 1. Synthesis of 4-{2-[(4-chloro-3-(trifluromethyl)phenyl)amino]-1-methyl-benzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-4-(methylamino)phenoxy]pyridine-2-carboxylate (1eq) in methanol was added 4-chloro-3-(trifluromethyl)benzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation

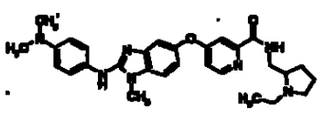
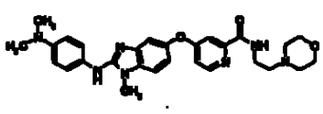
of .tert-butyl4-(2-{[4-chloro-3-(trifluromethyl)phenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-chloro-3-(trifluromethyl)phenylamino)-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: $MH^+ = 462$.

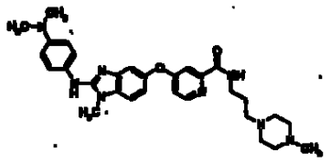
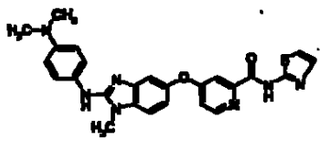
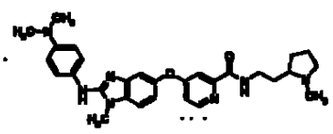
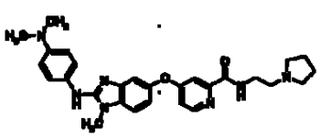
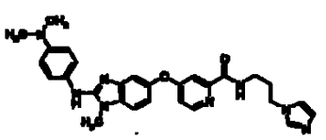
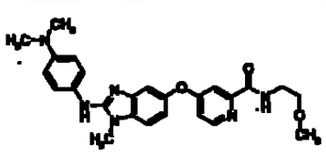
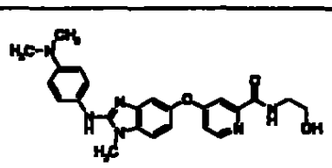
Step 2. Synthesis of [4-(2-{[4-chloro-3-(trifluromethyl)phenyl)amino-1-methyl-benzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)carboxamide

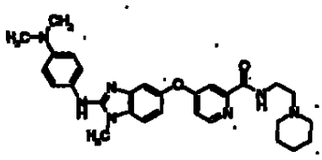
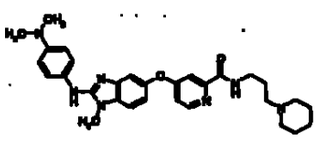
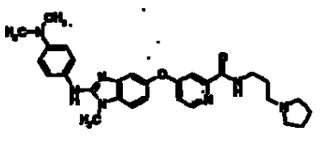
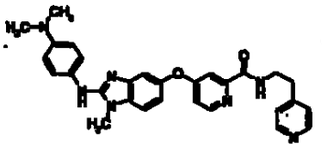
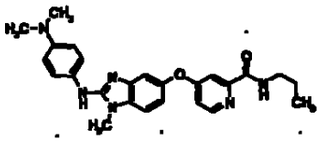
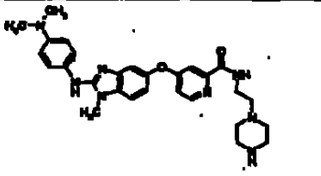
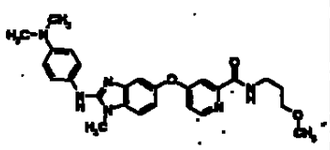
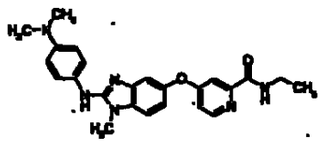
To 4-(2-{[4-chlro-3-(trifluromethyl)pheylamino)-1-methylbenzimidazol-5-yloxy)-pyridine-2-carboxylic acid(1eq) in tetrahydrofuran was added 2-piperidylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[4-chloro-3-trifluromethylphenyl]amino–1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-piperidylethyl)carboxamide. MS: $MH^+ = 558$.

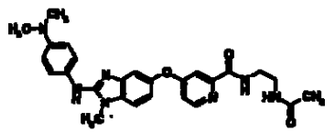
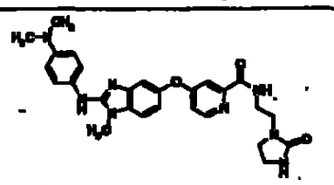
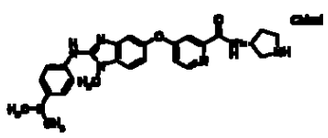
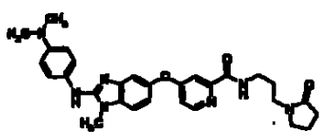
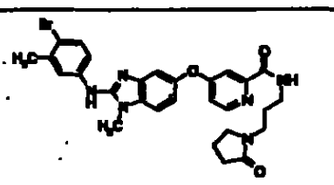
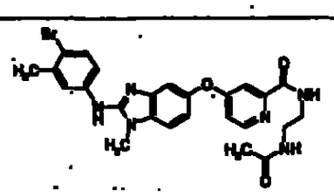
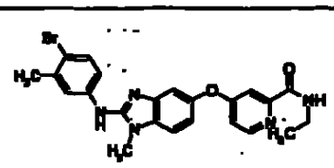
Each of the compounds 490-626 listed below in Table 6, were synthesized as indicated in the right hand column by the method described in one of the Examples 482-489.

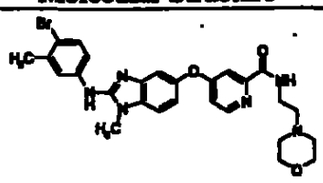
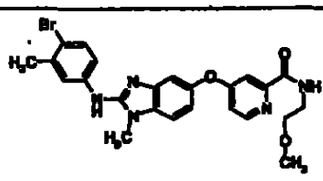
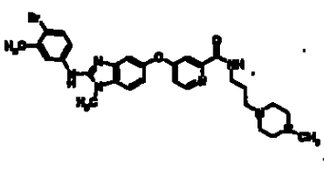
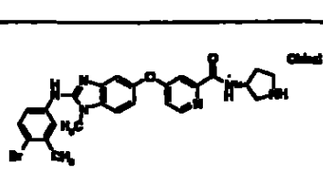
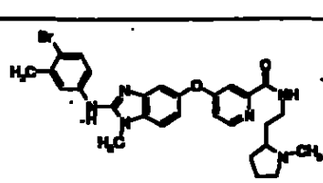
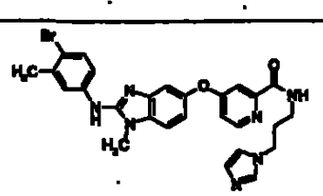
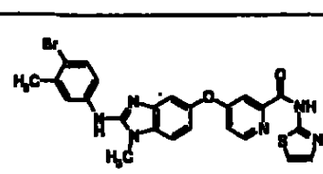
Table 6

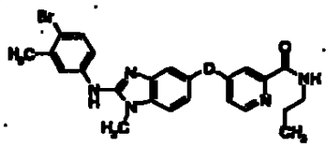
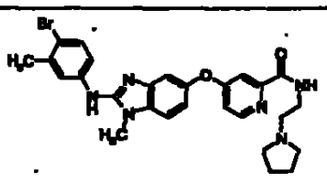
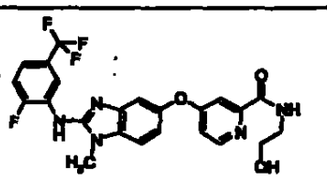
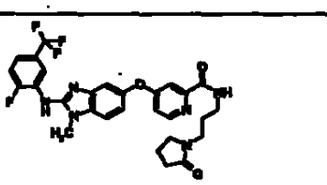
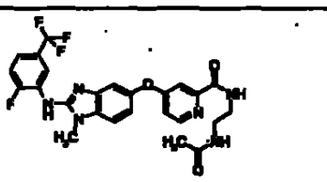
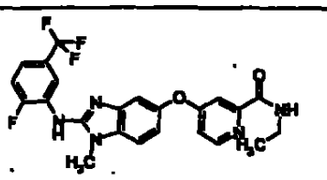
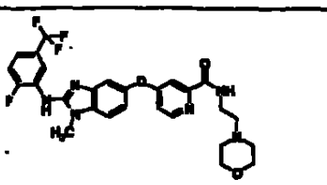
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
490		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[(1-ethylpyrrolidin-2-yl)-methyl]pyridine-2-carbox-amide	514.6	482
491		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-morpholin-4-ylethyl)-pyridine-2-carboxamide	516.6	482

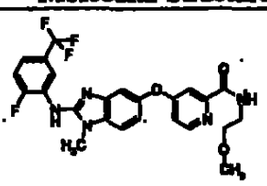
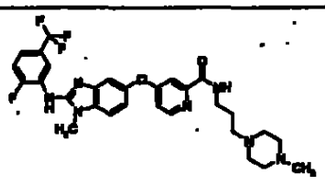
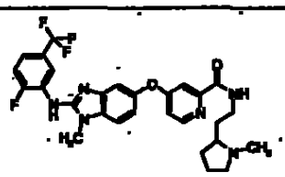
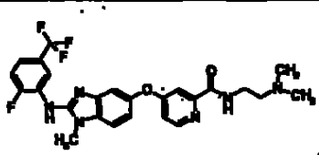
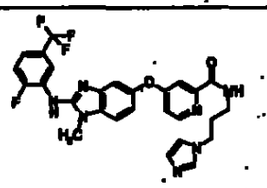
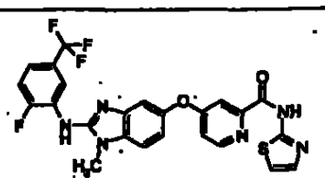
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
492		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	543.7	482
493		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-1,3-thiazol-2-ylpyridine-2-carboxamide	486.6	482
494		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	514.6	482
495		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyrrolidin-1-ylethyl)-pyridine-2-carboxamide	500.6	482
496		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(1H-imidazol-1-yl)-propyl]pyridine-2-carboxamide	511.6	482
497		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(methyloxy)ethyl]-pyridine-2-carboxamide	461.5	482
498		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-hydroxyethyl)-pyridine-2-carboxamide	447.5	482

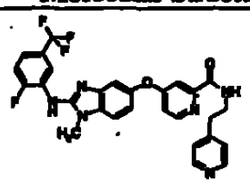
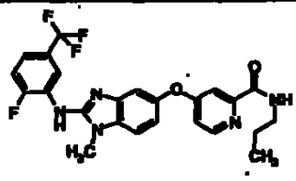
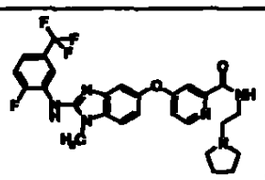
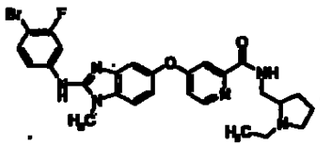
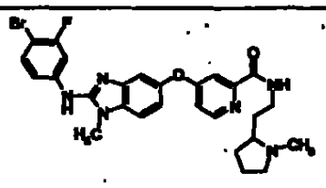
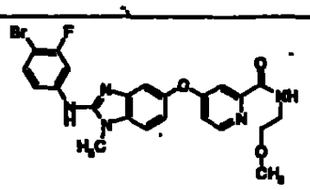
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
499		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-piperidin-1-ylethyl)-pyridine-2-carboxamide	514.6	482
500		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(3-piperidin-1-ylpropyl)-pyridine-2-carboxamide	528.7	482
501		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(3-pyrrolidin-1-ylpropyl)-pyridine-2-carboxamide	514.6	482
502		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	508.6	482
503		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-propylpyridine-2-carboxamide	445.5	482
504		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-piperazin-1-ylethyl)-pyridine-2-carboxamide	515.6	482
505		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(methyloxy)propyl]-pyridine-2-carboxamide	475.6	482
506		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-ethylpyridine-2-carboxamide	431.5	482

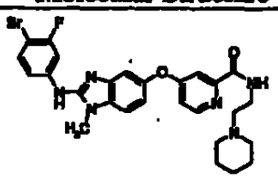
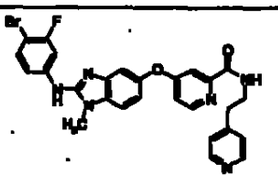
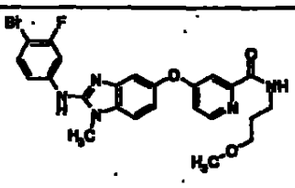
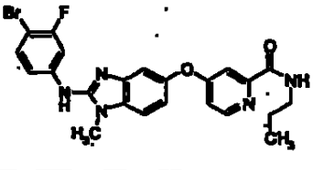
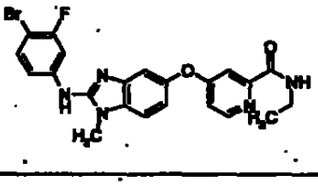
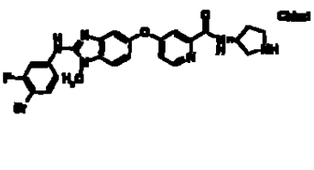
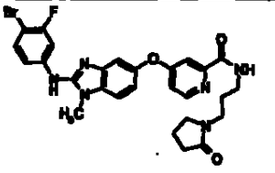
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
507		N-[2-(acetylamino)ethyl]-4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	488.6	482
508		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(2-oxoimidazolidin-1-yl)ethyl]pyridine-2-carboxamide	515.6	482
509		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[(3R)-pyrrolidin-3-yl]-pyridine-2-carboxamide	472.6	482
510		4-[(2-{[4-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	528.6	482
511		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	578.5	483
512		N-[2-(acetylamino)ethyl]-4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	538.4	483
513		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-ethylpyridine-2-carboxamide	481.4	483

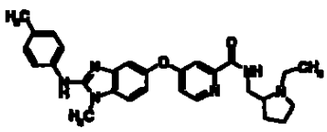
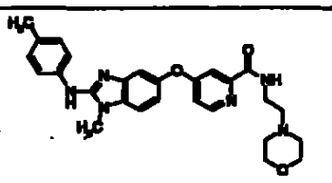
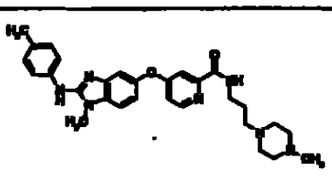
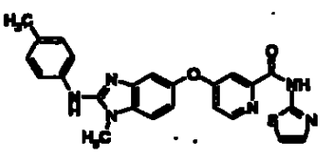
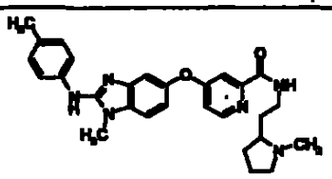
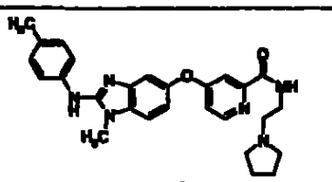
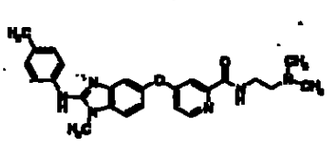
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
514		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	566.5	483
515		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(methyloxy)ethyl]pyridine-2-carboxamide	511.4	483
516		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	593.5	483
517		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[(3R)-pyrrolidin-3-yl]pyridine-2-carboxamide	522.4	483
518		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-pyridine-2-carboxamide	564.5	483
519		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(1H-imidazol-1-yl)propyl]pyridine-2-carboxamide	561.5	483
520		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-1,3-thiazol-2-ylpyridine-2-carboxamide	536.4	483

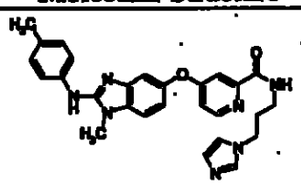
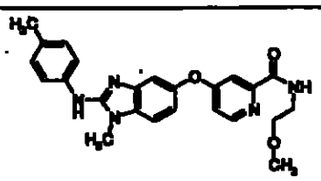
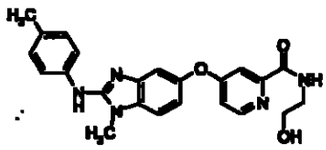
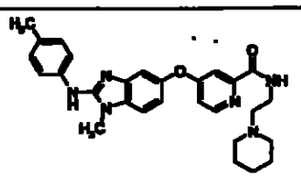
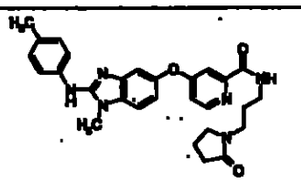
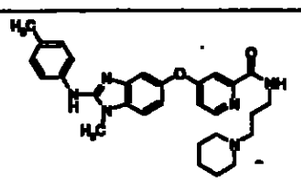
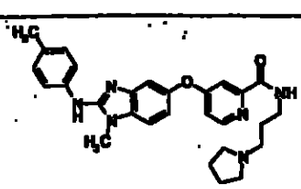
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
521		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-propylpyridine-2-carboxamide	495.4	483
522		4-({2-[(4-bromo-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-pyrrolidin-1-ylethyl)pyridine-2-carboxamide	550.5	483
523		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-hydroxyethyl)pyridine-2-carboxamide	490.4	484
524		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	571.5	484
525		N-[2-(acetylamino)ethyl]-4-[(2-{[2-fluoro-5-(trifluoromethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	531.5	484
526		N-ethyl-4-[(2-{[2-fluoro-5-(trifluoromethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	474.4	484
527		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-morpholin-4-yl-ethyl)pyridine-2-carboxamide	559.5	484

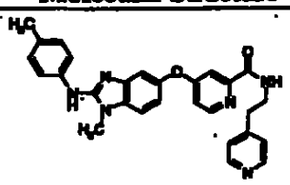
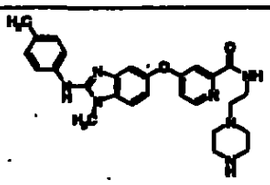
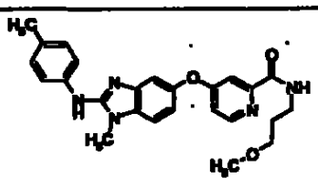
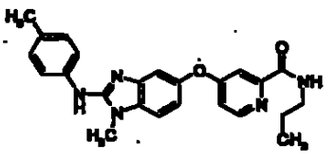
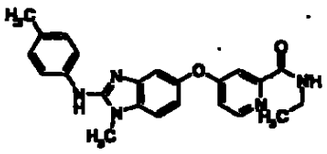
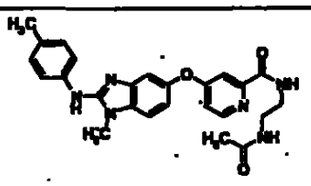
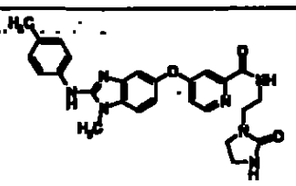
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
528		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(methyloxy)ethyl]-pyridine-2-carboxamide	504.5	484
529		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	586.6	484
530		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	557.6	484
531		N-[2-(dimethylamino)-ethyl]-4-[(2-{[2-fluoro-5-(trifluoromethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	517.5	484
532		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(1H-imidazol-1-yl)-propyl]pyridine-2-carboxamide	554.5	484
533		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-1,3-thiazol-2-ylpyridine-2-carboxamide	529.5	484

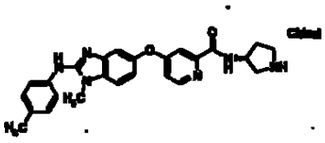
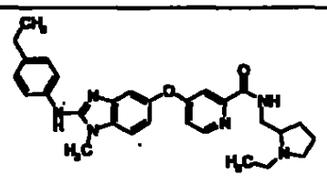
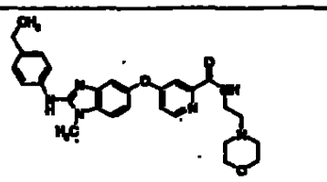
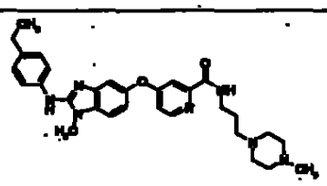
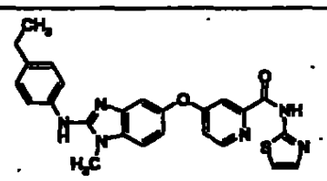
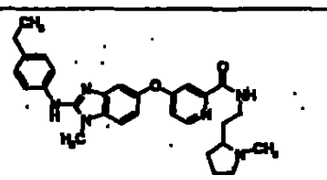
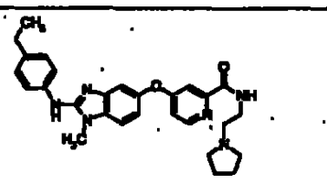
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
534		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	551.5	484
535		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-propylpyridine-2-carboxamide	488.5	484
536		4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyrrolidin-1-ylethyl)-pyridine-2-carboxamide	543.5	484
537		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[(1-ethylpyrrolidin-2-yl)methyl]pyridine-2-carboxamide	568.5	485
538		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]-pyridine-2-carboxamide	568.5	485
539		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(methyloxy)ethyl]pyridine-2-carboxamide	515.4	485

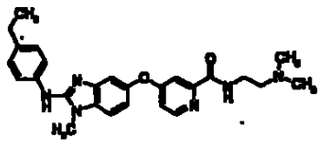
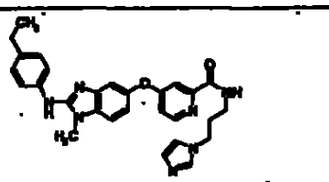
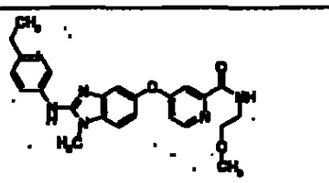
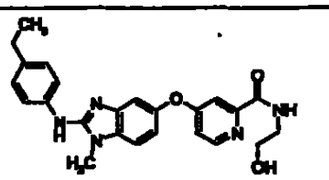
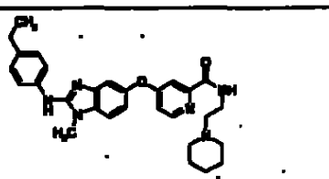
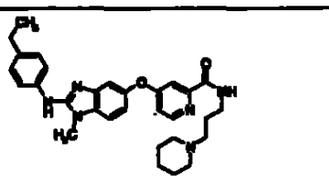
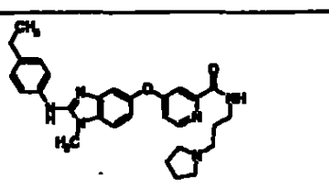
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
540		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-piperidin-1-ylethyl)pyridine-2-carboxamide	568.5	485
541		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-pyridin-4-ylethyl)pyridine-2-carboxamide	562.4	485
542		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(methyloxy)-propyl]pyridine-2-carboxamide	529.4	485
543		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-propylpyridine-2-carboxamide	499.4	485
544		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-ethylpyridine-2-carboxamide	485.3	485
545		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[(3R)-pyrrolidin-3-yl]pyridine-2-carboxamide	526.4	485
546		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	582.4	485

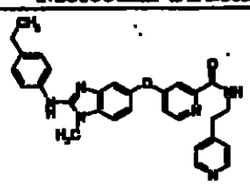
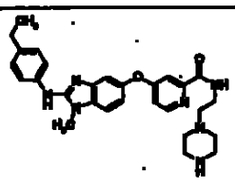
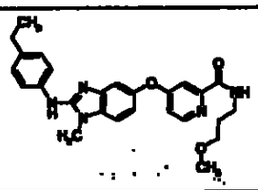
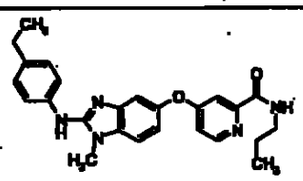
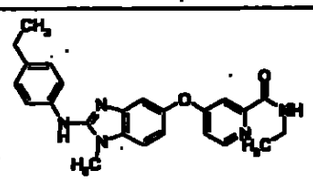
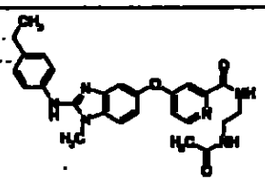
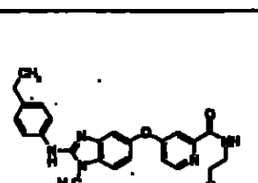
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
547		N-[(1-ethylpyrrolidin-2-yl)methyl]-4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	485.6	486
548		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	487.6	486
549		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	514.6	486
550		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-1,3-thiazol-2-ylpyridine-2-carboxamide	457.5	486
551		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	485.6	486
552		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-(2-pyrrolidin-1-ylethyl)pyridine-2-carboxamide	471.6	486
553		N-[2-(dimethylamino)-ethyl]-4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	445.5	486

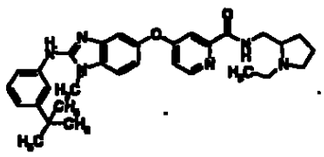
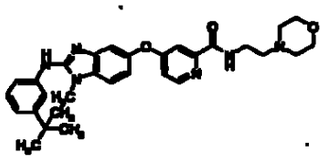
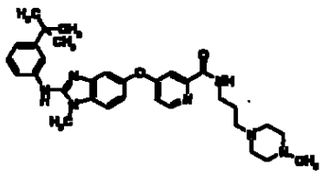
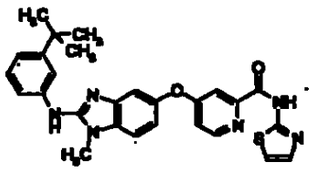
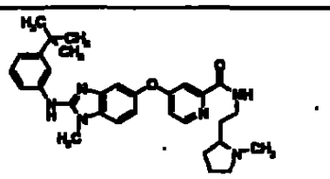
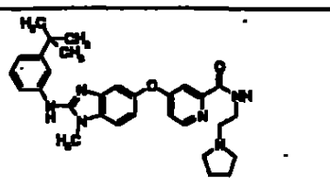
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
554		N-[3-(1H-imidazol-1-yl)propyl]-4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	482.6	486
555		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-[2-(methyloxy)ethyl]-pyridine-2-carboxamide	432.5	486
556		N-(2-hydroxyethyl)-4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	418.5	486
557		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-(2-piperidin-1-ylethyl)pyridine-2-carboxamide	485.6	486
558		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	499.6	486
559		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-(3-piperidin-1-ylpropyl)pyridine-2-carboxamide	499.6	486
560		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-(3-pyrrolidin-1-ylpropyl)pyridine-2-carboxamide	485.6	486

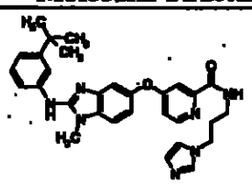
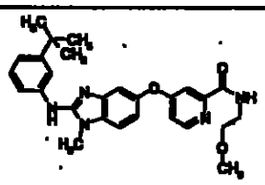
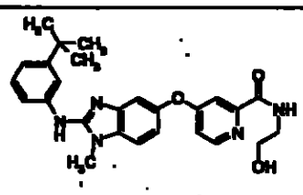
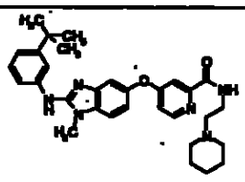
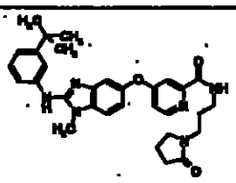
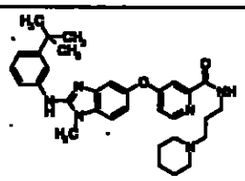
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
561		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-(2-pyridin-4-yl-ethyl)pyridine-2-carboxamide	479.6	486
562		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-(2-piperazin-1-yl-ethyl)pyridine-2-carboxamide	486.6	486
563		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-[3-(methyloxy)-propyl]pyridine-2-carboxamide	446.5	486
564		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-propylpyridine-2-carboxamide	416.5	486
565		N-ethyl-4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	402.5	486
566		N-[2-(acetylamino)ethyl]-4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	459.5	486
567		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-[2-(2-oxoimidazolidin-1-yl)ethyl]pyridine-2-carboxamide	486.5	486

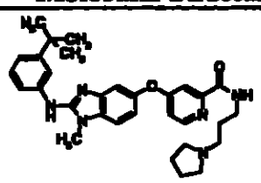
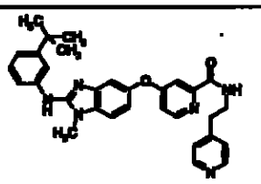
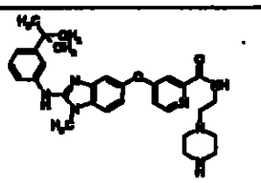
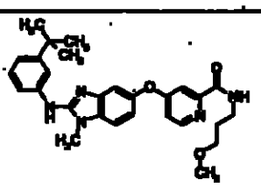
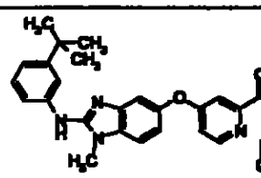
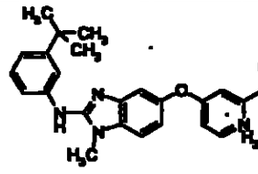
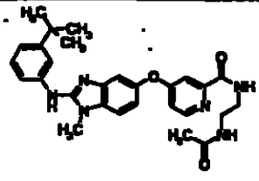
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
568		4-({1-methyl-2-[(4-methylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-N-[(3R)-pyrrolidin-3-yl]pyridine-2-carboxamide	443.5	486
569		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[(1-ethylpyrrolidin-2-yl)methyl]pyridine-2-carboxamide	499.6	487
570		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-morpholin-4-ylethyl)-pyridine-2-carboxamide	501.6	487
571		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	528.7	487
572		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-1,3-thiazol-2-ylpyridine-2-carboxamide	471.6	487
573		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	499.6	487
574		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-pyrrolidin-1-ylethyl)-pyridine-2-carboxamide	485.6	487

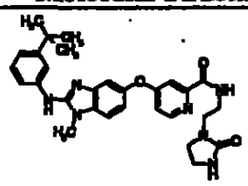
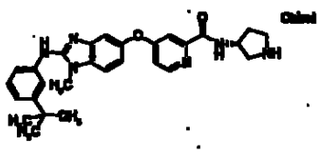
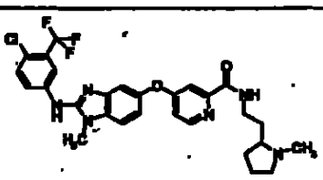
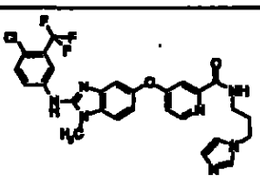
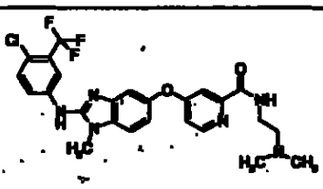
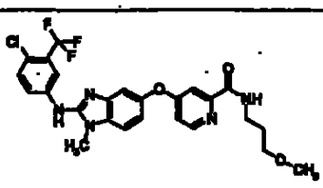
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
575		N-[2-(dimethylamino)-ethyl]-4-({2-[(4-ethyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridine-2-carbox-amide	459.6	487
576		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(1H-imidazol-1-yl)-propyl]pyridine-2-carbox-amide	496.6	487
577		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(methyloxy)ethyl]-pyridine-2-carboxamide	446.5	487
578		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	432.5	487
579		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-piperidin-1-ylethyl)-pyridine-2-carboxamide	499.6	487
580		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(3-piperidin-1-ylpropyl)-pyridine-2-carboxamide	513.7	487
581		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(3-pyrrolidin-1-yl-propyl)pyridine-2-carbox-amide	499.6	487

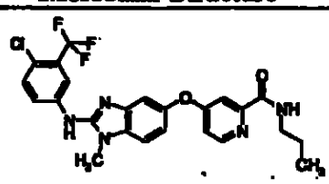
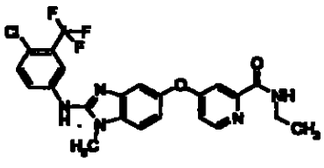
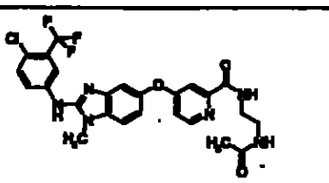
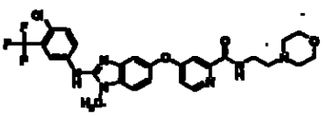
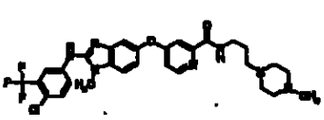
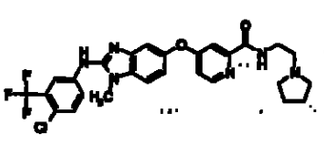
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
582		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	493.6	487
583		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-piperazin-1-ylethyl)-pyridine-2-carboxamide	500.6	487
584		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(methyloxy)propyl]-pyridine-2-carboxamide	460.5	487
585		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-propylpyridine-2-carboxamide	430.5	487
586		N-ethyl-4-({2-[(4-ethyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridine-2-carbox-amide	416.5	487
587		N-[2-(acetylamino)ethyl]-4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	473.5	487
588		4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(2-oxoimidazolidin-1-yl)ethyl]pyridine-2-carboxamide	500.6	487

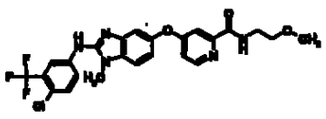
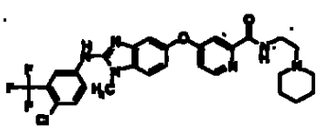
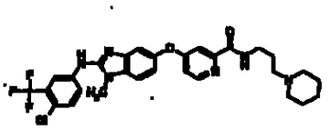
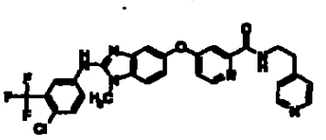
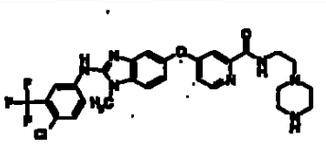
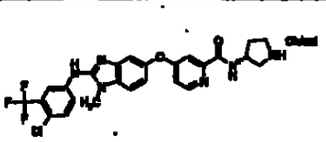
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
589		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[(1-ethyl-pyrrolidin-2-yl)methyl]-pyridine-2-carboxamide	527.7	488
590		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	529.7	488
591		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	556.7	488
592		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-1,3-thiazol-2-yl-pyridine-2-carboxamide	499.6	488
593		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]-pyridine-2-carboxamide	527.7	488
594		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyrrolidin-1-ylethyl)pyridine-2-carboxamide	513.7	488

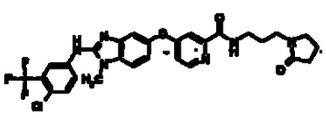
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
595		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(1H-imidazol-1-yl)propyl]pyridine-2-carboxamide	524.6	488
596		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(methyloxy)ethyl]pyridine-2-carboxamide	474.6	488
597		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-hydroxyethyl)pyridine-2-carboxamide	460.5	488
598		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-piperidin-1-yl-ethyl)pyridine-2-carbox-amide	527.7	488
599		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	541.7	488
600		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(3-piperidin-1-yl-propyl)pyridine-2-carbox-amide	541.7	488

Example	Molecular Structure	Name	MH+	Synthesized as in Example:
601		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(3-pyrrolidin-1-ylpropyl)pyridine-2-carboxamide	527.7	488
602		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyridin-4-ylethyl)pyridine-2-carboxamide	521.6	488
603		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-piperazin-1-ylethyl)pyridine-2-carboxamide	528.7	488
604		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(methyloxy)-propyl]pyridine-2-carboxamide	488.6	488
605		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-propylpyridine-2-carboxamide	458.6	488
606		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-ethylpyridine-2-carboxamide	444.5	488
607		N-[2-(acetylamino)ethyl]-4-[(2-{[3-(1,1-di-methylethyl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	501.6	488

Example	Molecular Structure	Name	MH+	Synthesized as in Example:
608		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(2-oxo-imidazolidin-1-yl)ethyl]-pyridine-2-carboxamide	528.6	488
609		4-[(2-{[3-(1,1-dimethyl-ethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[(3R)-pyrrolidin-3-yl]pyridine-2-carbox-amide	485.6	489
610		4-[(2-{[4-chloro-3-(tri-fluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	574.0	489
611		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(1H-imidazol-1-yl)propyl]pyridine-2-carboxamide	571.0	489
612		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(dimethylamino)-ethyl]pyridine-2-carbox-amide	534.0	489
613		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(methyloxy)propyl]-pyridine-2-carboxamide	534.9	489

Example	Molecular Structure	Name	MH+	Synthesized as in Example:
614		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-propylpyridine-2-carboxamide	504.9	489
615		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-ethylpyridine-2-carboxamide	490.9	489
616		N-[2-(acetylamino)ethyl]-4-[(2-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	547.9	489
617		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-morpholin-4-yl-ethyl)pyridine-2-carbox-amide	576.0	489
618		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	603.1	489
619		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyrrolidin-1-ylethyl)pyridine-2-carboxamide	560.0	489

Example	Molecular Structure	Name	MH+	Synthesized as in Example:
620		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(methyloxy)ethyl]-pyridine-2-carboxamide	520.9	489
621		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-piperidin-1-ylethyl)-pyridine-2-carboxamide	574.0	489
622		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(3-piperidin-1-yl-propyl)pyridine-2-carboxamide	588.0	489
623		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	568.0	489
624		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-piperazin-1-ylethyl)-pyridine-2-carboxamide	575.0	489
625		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[(3R)-pyrrolidin-3-yl]-pyridine-2-carboxamide	531.9	489

Example	Molecular Structure	Name	MH+	Synthesized as in Example:
626		4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	588.0	489

Example 627

Step 1. Synthesis of [4-(2-{[4-(chloromethyl)phenyl]carbonylamino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide

A solution of sodium thiocyanate (1eq) in acetone was added slowly in to a solution of 4-(chloromethyl)benzoylchloride (1eq) in acetone at 0°C. The mixture was then filtered in to a solution of {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) in acetone. Formation of N-acylthiourea was followed by LC/MS. The mixture was concentrated and taken in tetrahydrofuran and to it was added 1-ethyl-(3-dimethylaminopropyl)carbodimidehydrochloride (2eq) and stirred at ambient temperature for 16 h. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was then dried and concentrated to yield [4-(2-{[4-(chloromethyl)phenyl]carbonylamino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide. MS: $MH^+ = 449$.

Step 2. Synthesis of N-methyl{4-[1-methyl-2-({4-[(4methylpiperazinyl) methyl]phenyl} carbonylamino) benzimidazol-5-yloxy](2-pyridyl)}carboxamide.

To a solution of [4-(2-{[4-(chloromethyl)phenyl]carbonylamino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide (1eq) in tetrahydrofuran was added methylpiperazine (4eq) and stiired at ambient temperature for 16 h. The reaction mixture was concentrated and purified on preparative chromatography to yield N-methyl{4-[1-methyl-2-({4-[(4methylpiperazinyl) methyl]phenyl} carbonylamino) benzimidazol-5-yloxy](2-pyridyl)}carboxamide. MS: $MH^+ = 512$.

Example 628

Step 1. Synthesis of N-methyl[4-(1-methyl-2-{2-{4-[(4-methylpiperazinyl)-methylphenyl}-benzimidazol-5-yloxy)(2-pyridyl)]carboxamide

To a solution of {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) in tetrhydrofuran was added 4-(chloromethyl)benzoylchloride (1eq) and triethylamine (2eq). N-acylation is completed in 0.5 h. The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and to the crude product was added methylpiperazine (4eq) and tetrahydrofuran and stir for 16 h at ambient temperature. The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and taken in acetic acid and heated to 60°C for 3 h. Preparative chromatography yielded N-methyl[4-(1-methyl-2-{2-{4-[(4-methylpiperazinyl)methyl-phenyl}-benzimidazol-5-yloxy)(2-pyridyl)]carboxamide. MS: MH^+ =470.

Example 629

Step 1. Synthesis of 2-chloro-4-(3-pyridyl)pyrimidine

Nitrogen was bubbled through a solution of 2,4-dichloropyrimidine (1eq) in tetrahydrofuran and water (3:1) for 0.5 h. Bis(diphenylphosphino)ferrocene Palladium(II)chloride (0.05eq) followed by pyridine-3-boronic acid (1eq) and sodium carbonate (3eq) was added and the mixture was heated to 60°C for 16 h under nitrogen. The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried with sodium sulfate and concentrated. Purification on silica gel gave 2-chloro-4-(3-pyridyl)pyrimidine. MS: MH^+=190.

Step 2. Synthesis of 2-nitro-4-(4-(3-pyridyl)pyrimidin-2-yloxy)phenylamine

A solution of 4-amino-3-nitro-phenol (1eq) and 2-chloro-4-(3-pyridyl)pyrimidine (1eq) in N,N-dimethylformamide was microwaved at 150°C for 10 mins. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was concentrated and purified on silica gel to yield 2-nitro-4-(4-(3-pyridyl)pyrimidin-2-yloxy)phenylamine. MS: MH^+=309.

Step 3. Synthesis of 4-(4-(3-pyridyl)pyrimidin-2-yloxy)benzene-1,2-diamine

The mixture containing 2-nitro-4-(4-(3-pyridyl)pyrimidin-2-yloxy)phenylamine in methanol with catalytic amount of 10% Pd/C was hydrogenated until disappearance of yellow color to yield 4-(4-(3-pyridyl)pyrimidin-2-yloxy)benzene-1,2-diamine. MS: MH^+ =279.

Step 3. Synthesis of {4-[(4-methylpiperazinyl)methyl]phenyl}-N-[5-(4-(3-pyridyl)pyrimidin-2-yloxy)benzimidazol-2-yl]carboxamide.

A solution of sodium thiocyanate (1eq) in acetone was added slowly in to a solution of 4-(chloromethyl)benzoylchloride (1eq) in acetone at 0°C. The mixture was then filtered in to a solution of 4-(4-(3-pyridyl)pyrimidin-2-yloxy)benzene-1,2-diamine (1eq) in acetone. Formation of N-acylthiourea was followed by LC/MS. The mixture was concentrated and taken in tetrahydrofuran and to it was added 1-ethyl-(3-dimethylaminopropyl)carbodimidehydrochloride (2eq) and stirred at ambient temperature for 16 h. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was then dried and concentrated to yield [4-(chloromethyl)phenyl]-N-[5-(4-(3-pyridyl)pyrimidin-2-yloxy)benzimidazol-2-yl]carboxamide. It was taken in tetrahydrofuran and added methylpiperazine (4eq) and stirred at ambient temperature for 16 h. The reaction mixture was concentrated and purified on preparative chromatography to yield {4-[(4-methylpiperazinyl) methyl]phenyl}-N-[5-(4-(3-pyridyl)pyrimidin-2-yloxy)benzimidazol-2-yl]carboxamide. MS: MH^+ =520.

Example 630

Step 1. Synthesis of 4-ethyl-1-[(4-nitrophenyl)methylpiperazine

To 4-(chloromethyl)-1-nitrobenzene(1eq) in tetrahydrofuran was added Ethylpiperazine (3eq) and stir for 16 h at ambient temperature. Concentrating and passing through a plug of silica gave 4-ethyl-1-[(4-nitrophenyl)methylpiperazine. MS: $MH^+ = 249$

Step 2. Synthesis of 4-[(4-ethylpiperazinyl)methyl]phenylamine

The mixture containing 4-ethyl-1-[(nitrophenyl)methylpiperazine in methanol with catalytic amount of 10% Pd/C was hydrogenated to yield 4-[(4-ethyl-piperazinyl)methyl]phenylamine. MS: $MH^+ = 219$.

Step 3. Synthesis of 4-[(4-ethylpiperazinyl)methyl]benzeneisothiocyanate

To 4-[(4-ethylpiperazinyl)methyl]phenylamine in acetone at 0°C was added sodium bicarbonate (2eq) and thiophosgene (2eq). The mixture was brought to ambient temperature and concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium bicarbonate and sodium sulfate and concentrated to yield 4-[(4-ethylpiperazinyl)methyl]benzeneisothiocyanate. MS: $MH^+ = 261$.

Step 4. Synthesis of [4-[(2-{[4-ethylpiperazinyl)methyl]phenyl]amino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide

To 4-[(4-ethylpiperazinyl)methyl]benzeneisothiocyanate(1eq) in methanol was added {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) and heated to 60°C for 16 h. Preparative chromatography yielded [4-[(2-{[4-ethylpiperazinyl)methyl]phenyl]amino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide. MS: MH^+ = 499.

Example 631

Step 1. Synthesis of 4-Ethyl-1-(4-nitrophenyl)piperazine

To 4-fluro-1-nitrobenzene(1eq) in N,N-dimethylformamide was added Ethyl piperazine (2eq) and N,N-diisopropylethyl amine (2eq) and heated at 80°C for 16 h. Concentrated the resultant mixture and partitioned between ethyl acetate and water. The organic layer was then washed with brine and dried with sodium sulfate and concentrated. Passed through a plug of silica to yield 4-Ethyl-1-(4-nitrophenyl)piperazine. MS: MH^+ = 235.

Step 2. Synthesis of 4-(4-ethylpiperazinyl)phenylamine

The mixture containing 4-ethyl-1-(4-nitrophenyl)piperazine in methanol with catalytic amount of 10%Pd/C was hydrogenated to yield 4-(4-ethylpiperazinyl)phenylamine. MS: MH^+ = 205.

Step 3. Synthesis of 4-(4-ethylpiperazinyl)benzeneisothiocyanate

To 4-(4-ethylpiperazinyl)phenylamine in acetone at 0°C was added sodium bicarbonate (2eq) and thiophosgene (2eq). The mixture was brought to ambient temperature and concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium bicarbonate and sodium sulfate and concentrated to yield 4-(4-ethylpiperazinyl)benzeneisothiocyanate. MS: MH^+ = 247.

Step 3. Synthesis of [4-(2-{[4-ethylpiperazinyl)phenyl]amino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide

To 4-(4-ethylpiperazinyl)benzeneisothiocyanate (1eq) in methanol was added {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) and heated to 60°C for 16 h. Preparative purification yielded [4-(2-{[4-ethylpiperazinyl)phenyl]-amino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide. MS: MH^+ = 485.

Example 632

Step 1. Synthesis of 4-(2-bromoethyl)-1-nitrobenzene

To 4-(2-bromoethyl)-1-nitrobenzene(1eq) in tetrahydrofuran was added morpholine (3eq) and stir for 16 h at ambient temperature. Concentrating and passing through a plug of silica gave 4-[2-(4-nitrophenyl)ethylmorpholine. MS: $MH^+ = 236$.

Step 2. Synthesis of 4-(2-morpholin-4-ylethyl)phenylamine

The mixture containing 4-[2-(4-nitrophenyl)ethyl]morpholine in methanol with catalytic amount of 10%Pd/C was hydrogenated to yield 4-(2-morpholin-4-ylethyl)phenylamine. MS: $MH^+ = 206$.

Step 3. Synthesis of 4-(2-morpholin-4-ylethyl)benzeneisothiocyanate

To 4-(2-morpholin-4-ylethyl)phenylamine in acetone at 0°C was added sodium bicarbonate (2eq) and thiophosgene (2eq). The mixture was brought to ambient temperature and concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium bicarbonate and sodium sulfate and concentrated to yield 4(2-morpholin-4-ylethyl)benzeneisothiocyanate. MS: $MH^+ = 252$.

Step 4. Synthesis of N-methyl[4-(1-methyl-2-{[4-(2-morpholin-4-ylethyl)phenyl]amino}-benzimidazol-5-oxy)(2-pyridyl)]carboxamide

To 4(2-morpholin-4-ylethyl)benzeneisothiocyanate (1eq) in methanol was added {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) and stirred at ambient temperature for 16 h. The corresponding thiourea formation was followed by LC/MS. To it was the added iodomethane(1eq) and heated to 60°C for 3h. Concentration followed by preparative chromatography yielded N-methyl[4-(1-methyl-2-{[4-(2-morpholin-4-ylethyl)phenyl]amino}-benzimidazol-5-oxy)(2-pyridyl)]carboxamide. MS: $MH^+ = 486$.

Example 633

Step 1. Synthesis of [(4-nitrophenyl)ethyl]benzylamine

To a solution of 1-(4-nitrophenyl)ethan-1-one (1eq) and phenylmethylamine (1eq) in methanol was added sodiumtriacetoxyborohydride (1.2eq). The resulting mixture was stirred at ambient temperature for 16 h. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative purification yielded [(4-nitrophenyl) ethyl]benzylamine. MS: $MH^+ = 256$.

Step 2. Synthesis of [(4-aminophenyl)ethyl]benzylamine

The mixture containing [(4-nitrophenyl) ethyl]benzylamine in methanol with catalytic amount of 10%Pd/C was hydrogenated until disappearance of yellow color to yield [(4-aminophenyl)ethyl]benzylamine. MS: MH^+=226.

Step 3. Synthesis of 4-{[benzylamino]ethyl}benzeneisothiocyanate

To [(4-nitrophenyl) ethyl]benzylamine in acetone at 0°C was added sodium bicarbonate (2eq) and thiophosgene (2eq). The mixture was brought to ambient temperature and concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium bicarbonate and sodium sulfate and concentrated to yield 4-{[benzylamino]ethyl}benzeneisothiocyanate. MS: MH^+=268.

Step 4. Synthesis of N-methyl(4-{1-methyl-2-2[(4-{[benzylamino]ethyl}-phenyl)amino)benzimidazol-5-yloxy)-(2-pyridyl))carboxamide

To a solution of [4-(3,4-diaminophenoxy)(2-pyridyl))]-N-methylcarboxamide(1eq) in methanol was added 4-{[benzylamino]ethyl}benzeneisothiocyanate (1eq) and heated to 60°C for 3h. Preparative chromatography yielded N-methyl(4-{1-methyl-2-2-[(4-{[benzylamino] ethyl}phenyl) amino)benzimidazol-5-yloxy)-(2-pyridyl))-carboxamide. MS: MH^+=506.

Example 634

Step 1. Synthesis of (5-fluro-2-nitrophenyl)methylamine

A solution of 5-fluro-2-nitrophenylamine (1eq) in methylenechloride was treated with trifluoroacetic anhydride (1eq) and stirred for 10 minutes at 0°C. The mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated and washed with water , brine, dried and evaporated. To the solution of the trifluoroacetamide (1eq) in a mixture of toluene, acetonitrile and sodium hydroxide solution (50%) was added benzyltrimethylammonium chloride (1eq) and dimethyl sulfate (1.2eq). The biphasic mixture was stirred overnight at room temperature and evaporated. The mixture was taken up in ethyl acetate, washed with water, brine, dried and evaporated. The crude was purified by column chromatography eluting with 1:1 hexanes and ethyl acetate to afford (5-fluro-2-nitrophenyl)methylamine. MS: MH^+=170.

Step 2. Synthesis of {4-[4-amino-3-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide

The mixture containing 5-fluro-2-nitrophenylamine (1eq), Potassium bis(trimethylsilyl)amide (2eq) was stirred in dimethylformamide for 2 hours at room temperature. To this mixture was added (3-hydroxyphenyl)-N-methylcarboxamide (1eq) and Potassium carbonate (1.2eq) and stirred at 90°C for 16 h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried, filtered and concentrated in vacuum to give brown solid. Purification on silica gel gave N-methyl{4-[3-(methylamino)-4-nitro-phenoxy](2-pyridyl))carboxamide. It was taken in methanol and hydrogenated with catalytic amount of 10%Pd/C to give {4-[4-amino-3-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide. MS: MH^+=272.

Step 3. Synthesis of (4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-6-yloxy)-(2-pyridyl)-N-methylcarboxamide

A solution of the {4-[4-amino-3-(methylamino)phenoxy](2-pyridyl)}-N-methyl-carboxamide(1eq) in methanol was treated with 4 -bromophenylisothiocyanate (1eq) and stirred at 60°C for 2 hours. The reaction mixture was cooled down to room temperature and iodomethane (1eq) was added and stirred overnight at 60°C. The reaction was concentrated and preparative chromatography gave (4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-6-yloxy)-(2-pyridyl)-N-methylcarboxamide. MS: MH^+=452.

Example 635

Step 1. Synthesis of ((5-aminobenzimidazol-2-yl)(4-bromophenylamine)

A solution of the 4-nitrobenzene-1,2-diamine in methanol was treated with 4-bromo phenyl isothiocyanate (1eq) and stirred at 60°C for 2 hours. The reaction mixture was cooled down to room temperature and iodomethane (1eq) was added and stirred overnight at 60°C. The reaction was concentrated and purified on silica gel to yield (4-bromophenyl)(5-nitrobenzimidazol-2-yl)amine. The product was taken in methanol and hydrogenated with catalytic amount of 10%Pd/C to give ((5-aminobenzimidazol-2-yl)(4-bromophenylamine). MS: MH^+=302.

Step 2. Synthesis of [4-({2-[(4-bromophenyl)amino}benzimidazol-5-yl}amino)-(2-pyridyl_-N-methylcarboxamide

To a solution of ((5-aminobenzimidazol-2-yl)(4-bromophenylamine(1eq) in N,N-dimethylformamide was added sodium hydride (2eq) and the mixture was microwaved

for 8mins at 220°C. The reaction mixture was partitioned between ethyl acetate and water and the organic layer was dried with sodium sulfate and concentrated. Preparative chromatography yielded [4-({2-[(4-bromophenyl)amino}benzimidazol-5-yl}amino)(2-pyridyl_-N-methylcarboxamide. MS: MH^+ =437.

Example 636

Step 1. Synthesis of (4-{2-[(4-bromophenyl)methyl]-1-methylbenzimidazol-5-yloxy)-(2-pyridyl))-N-methylcarboxamide

To 4-bromophenyl acetic acid (1eq) in dichoromethane containing a drop of N,N-dimethyl formamide at 0°C was added oxalyl chloride (1.2eq). The resulting mixture was then brought to ambient temperature and stirred for 2 h. The mixture was concentrated and to it was added tetrahydrofuran and [4-(3,4-diaminophenoxy)(2-pyridyl)]-N-methylcarboxamide (1eq) and triethyl amine (1eq) and stirred for 2 h. Formation of the N-acylated product was followed by LC/MS. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium sulfate and concentrated and taken in acetic acid and heated to 60°C for 2 h. Preparative chromatography yielded (4-{2-[(4-bromophenyl)methyl]-1-methylbenzimidazol-5-yloxy)-(2-pyridyl))-N-methylcarboxamide. MS: MH^+ = 451.

Example 637

Step 1. Synthesis of 4-({1-methyl-5-[2-(N-methylcarbamoyl)(4-pyridyl-oxy))]benzimidazol-2-yl}amino)benzoic acid

To {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) in methanol was added 4-isothiocyanatobenzoic acid (1eq) and stirred at 60°C for 3h. To it was then added iodomethane (1eq) and heated to 60°C for 3h. and concentrated the solvent and purified on silica gel to yield 4-({1-methyl-5-[2-(N-methylcarbamoyl)(4-pyridyloxy))]benzimidazol-2-yl}amino)benzoic acid. MS: MH^+ = 417.

Step 2. Synthesis of N-methyl[4-(1-methyl-2-{[4-(2-morpholin-4-ylethyl)phenyl]-amino-benzimidazol-5-oxy)(2-pyridyl)]carboxamide CHIR-164277

To 4-({1-methyl-5-[2-(N-methylcarbamoyl)(4-pyridyloxy))]benzimidazol-2-yl}-amino)benzoic acid (1eq) in tetrahydrofuran was added morpholine (2eq) and N,N-diisopropylethylamine(4eq) and HBTU(2eq) and stir at ambient temperature for 16 h.

The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried with sodium sulfate. Preparative chromatography gave N-methyl[4-(1-methyl-2-{[4-(2-morpholin-4-ylethyl)phenyl]-amino-benzimidazol-5-oxy)(2-pyridyl)]carboxamide. MS: MH^+ = 529.

Example 638

Step 1. Synthesis of 3-({1-methyl-5- [2-(N-methylcarbamoyl)(4-pyridyloxy))] benzimidazol-2-yl} amino) benzoic acid

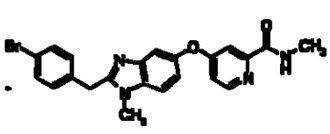
To 4-[3-amino-4- (methylamino) phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) in methanol was added 3-isothiocyanatobenzoic acid (1eq) and stirred at 60°C for 3h. To it was then added iodomethane (1eq) and heated to 60°C for 3h and concentrated the solvent and purified on silica gel to yield 3-({1-methyl-5- [2-(N-methylcarbamoyl)(4-pyridyloxy))] benzimidazol-2-yl} amino)benzoic acid. MS: MH+ = 417.

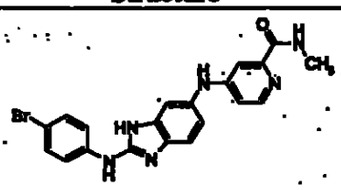
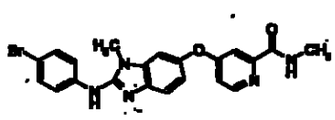
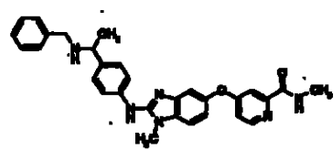
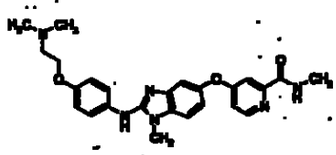
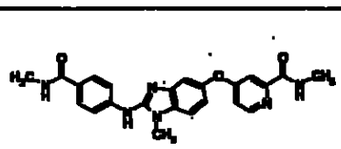
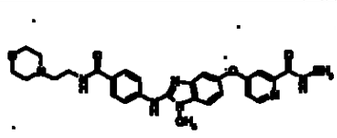
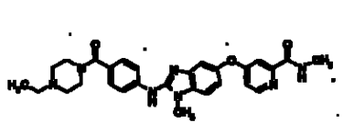
Step 2. Synthesis of N-methyl[3-(1-methyl-2-{[4-(2-morpholin-4-ylethyl)phenyl]-amino-benzimidazol-5-oxy)(2-pyridyl)]carboxamide

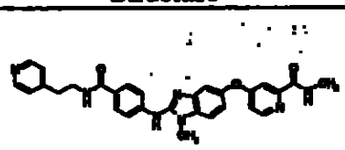
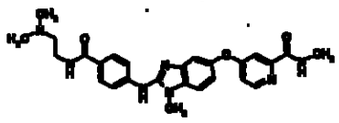
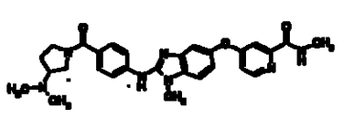
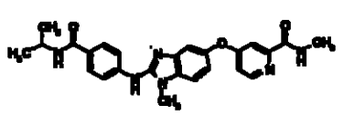
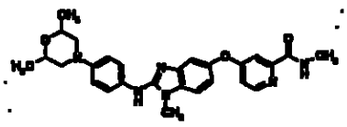
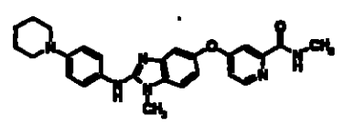
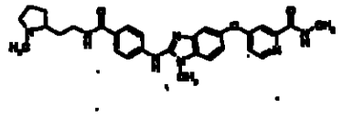
To 3-({1-methyl-5-[2-(N-methylcarbamoyl)(4-pyridyloxy))]benzimidazol-2-yl}-amino)benzoic acid (1eq) in tetrahydrofuran was added morpholine (2eq) and N,N-diisopropylethylamine (4eq), EDCI (2eq), HOAT(1.2eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried with sodium sulfate. Preparative chromatography gave N-methyl[3-(1-methyl-2-{[4-(2-morpholin-4-ylethyl)-phenyl]amino-benzimidazol-5-oxy)(2-pyridyl)]carboxamide. MS: MH+ = 529.

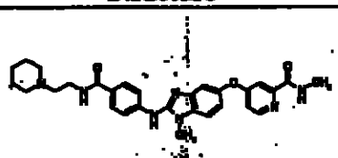
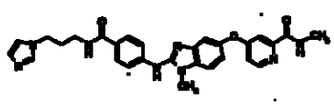
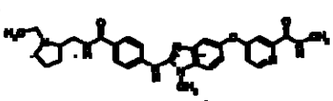
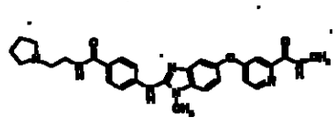
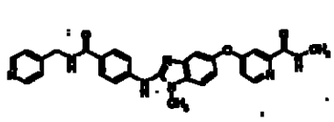
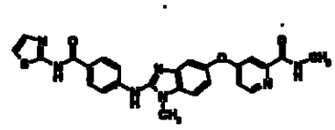
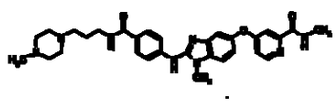
Each of the compounds 639-698, listed in Table 7 were synthesized as indicated in the right hand column by the method described in one of the Examples 627-638 or as otherwise indicated.

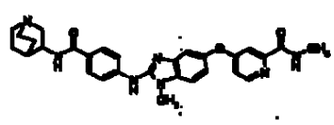
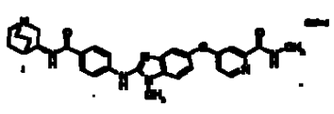
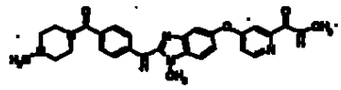
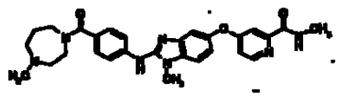
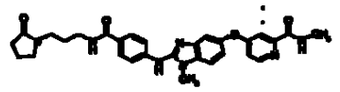
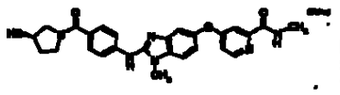
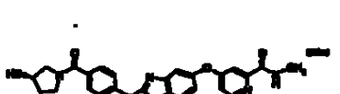
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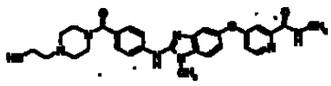
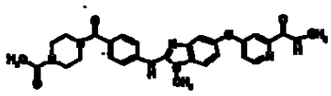
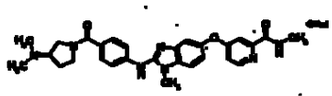
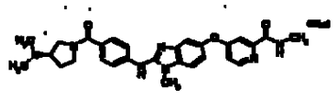
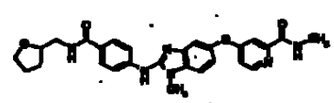
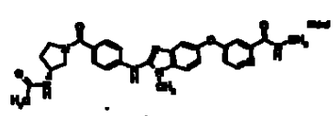
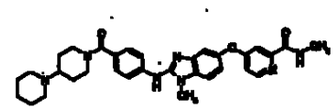
Example	Structure	Name	MH+	Synthesis as in Example:
639		4-({2-[(4-bromophenyl)-methyl]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carbox-amide	452.3	636

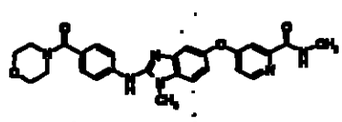
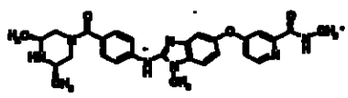
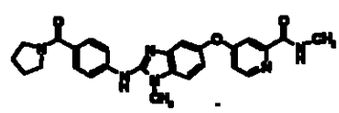
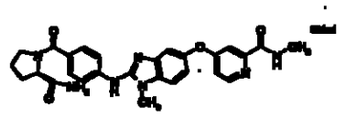
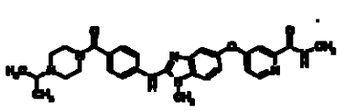
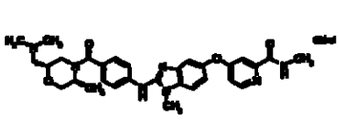
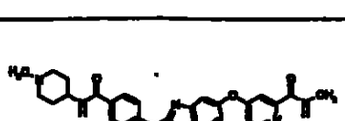
Example	Structure	Name	MH+	Synthesis as in Example:
640		4-({2-[(4-bromophenyl)-amino]-1H-benzimidazol-6-yl}amino)-N-methylpyridine-2-carboxamide	438.3	635
641		4-({2-[(4-bromophenyl)-amino]-1-methyl-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide	453.3	634
642		N-methyl-4-({1-methyl-2-[(4-{1-[(phenylmethyl)-amino]ethyl}phenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	507.6	633
643		4-({2-[(4-{[2-(dimethyl-amino)ethyl]oxy}phenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carbox-amide	461.5	631
644		N-methyl-4-{[1-methyl-2-({4-[(methylamino)-carbonyl]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	431.5	637
645		N-methyl-4-({1-methyl-2-[(4-{[(2-morpholin-4-yl-ethyl)amino]carbonyl}-phenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	530.6	637
646		4-{[2-({4-[(4-ethylpiperazin-1-yl)carbonyl]phenyl}-amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carbox-amide	514.6	637

Example	Structure	Name	MH+	Synthesis as in Example:
647		N-methyl-4-({1-methyl-2-[(4-{[(2-pyridin-4-ylethyl)-amino]carbonyl}phenyl)amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	522.6	637
648		4-[(2-{[4-({[2-(dimethyl-amino)ethyl]amino}-carbonyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	488.6	637
649		4-({2-[(4-{[3-(dimethyl-amino)pyrrolidin-1-yl]-carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	514.6	637
650		N-methyl-4-({1-methyl-2-[(4-{[(1-methylethyl)amino]-carbonyl}phenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	459.5	637
651		4-[(2-{[4-(2,6-dimethyl-morpholin-4-yl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carbox-amide	487.6	120a
652		N-methyl-4-({1-methyl-2-[(4-piperidin-1-ylphenyl)-amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carbox-amide	457.5	120a
653		N-methyl-4-[(1-methyl-2-{[4-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}carbonyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	528.6	637

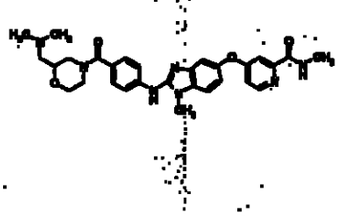
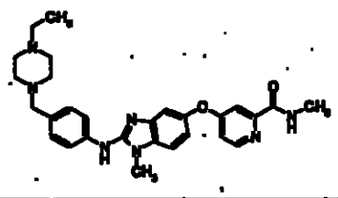
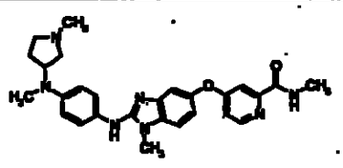
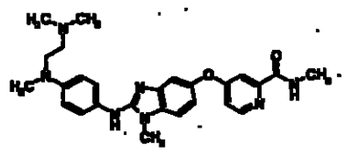
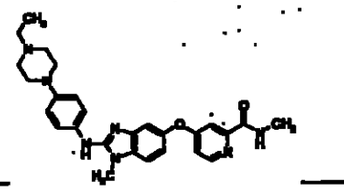
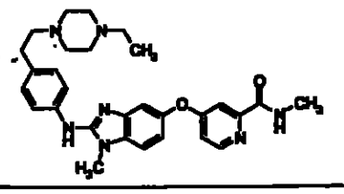
Example	Structure	Name	MH+	Synthesis as in Example:
654		N-methyl-4-({1-methyl-2-[(4-{[(2-piperidin-1-ylethyl)-amino]carbonyl}phenyl)amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	528.6	637
655		4-[(2-{[4-({[3-(1H-imidazol-1-yl)propyl]amino}carbonyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carbox-amide	525.6	637
656		4-[(2-{[4-({[(1-ethyl-pyrrolidin-2-yl)methyl]-amino}carbonyl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carbox-amide	528.6	637
657		N-methyl-4-({1-methyl-2-[(4-{[(2-pyrrolidin-1-yl-ethyl)amino]carbonyl}-phenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	514.6	637
658		N-methyl-4-({1-methyl-2-[(4-{[(pyridin-4-ylmethyl)-amino]carbonyl}phenyl)-amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	508.6	637
659		N-methyl-4-{[1-methyl-2-({4-[(1,3-thiazol-2-yl-amino)carbonyl]phenyl}amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	500.6	637
660		N-methyl-4-[(1-methyl-2-{[4-({[3-(4-methylpiperazin-1-yl)propyl]amino}carbonyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	557.7	637

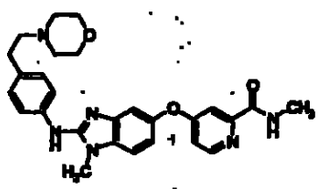
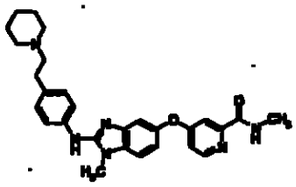
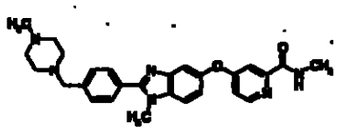
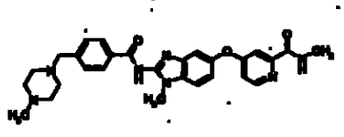
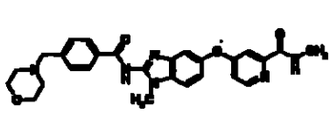
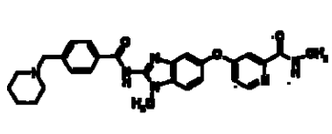
Example	Structure	Name	MH+	Synthesis as in Example:
661		4-{[2-({4-[(1-aza-bicyclo[2.2.2]oct-3-ylamino)-carbonyl]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	526.6	637
662		4-({2-[(4-{[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	526.6	637
663		N-methyl-4-{[1-methyl-2-({4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	500.6	637
664		N-methyl-4-{[1-methyl-2-({4-[(4-methyl-1,4-diazepan-1-yl)carbonyl]phenyl}-amino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	514.6	637
665		N-methyl-4-[(1-methyl-2-{[4-({[3-(2-oxopyrrolidin-1-yl)propyl]amino}carbonyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	542.6	637
666		4-({2-[(4-{[(3R)-3-hydroxy-pyrrolidin-1-yl]carbonyl}-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	487.5	637
667		4-({2-[(4-{[(3S)-3-hydroxy-pyrrolidin-1-yl]carbonyl}-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	487.5	637

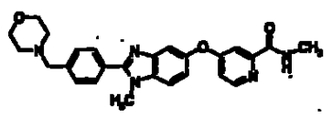
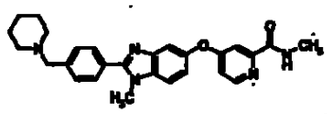
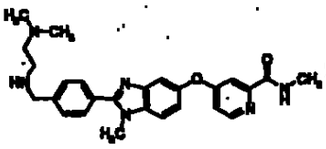
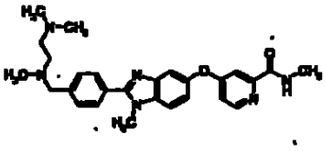
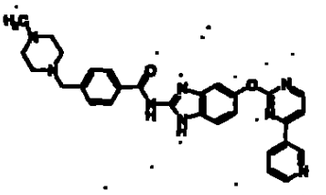
Example	Structure	Name	MH+	Synthesis as in Example:
668		4-({2-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	530.6	637
669		4-{[2-({4-[(4-acetylpiperazin-1-yl)carbonyl]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	528.6	637
670		4-({2-[(4-{[(3R)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	514.6	637
671		4-({2-[(4-{[(3S)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	514.6	637
672		N-methyl-4-({1-methyl-2-[(4-{[(tetrahydrofuran-2-ylmethyl)amino]carbonyl}phenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	501.6	637
673		4-({2-[(4-{[(3R)-3-(acetylamino)pyrrolidin-1-yl]carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	528.6	637
674		4-[(2-{[4-(1,4'-bipiperidin-1'-ylcarbonyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	568.7	637

Example	Structure	Name	MH+	Synthesis as in Example:
675		N-methyl-4-[(1-methyl-2-{[4-(morpholin-4-yl-carbonyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	487.5	637
676		4-({2-[(4-{[(3R,5S)-3,5-dimethylpiperazin-1-yl]-carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	514.6	637
677		N-methyl-4-[(1-methyl-2-{[4-(pyrrolidin-1-yl-carbonyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	471.5	637
678		4-({2-[(4-{[(2R)-2-(amino-carbonyl)pyrrolidin-1-yl]-carbonyl}phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	514.6	637
679		N-methyl-4-({1-methyl-2-[(4-{[4-(1-methylethyl)-piperazin-1-yl]carbonyl}-phenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	528.6	637
680		4-[(2-{[4-({(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-carbonyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	558.7	637
681		N-methyl-4-({1-methyl-2-[(4-{[(1-methylpiperidin-4-yl)amino]carbonyl}phenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	514.6	637

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Example	Structure	Name	MH+	Synthesis as in Example:
682		4-[(2-{[4-({2-[(dimethylamino)methyl]morpholin-4-yl}carbonyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	544.6	637
683		4-{[2-({4-[(4-ethylpiperazin-1-yl)methyl]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	500.6	630
684		N-methyl-4-{[1-methyl-2-{4-[methyl(1-methyl-pyrrolidin-3-yl)amino]-phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	486.6	631
685		4-{[2-({4-[[2-(dimethyl-amino)ethyl](methyl)amino]-phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	474.6	631
686		4-[(2-{[4-(4-ethylpiperazin-1-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	486.6	631
687		4-{[2-({4-[2-(4-ethylpiperazin-1-yl)ethyl]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	514.6	632

Example	Structure	Name	MH+	Synthesis as in Example:
688		N-methyl-4-[(1-methyl-2-{[4-(2-morpholin-4-ylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	487.6	632
689		N-methyl-4-[(1-methyl-2-{[4-(2-piperidin-1-ylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	485.6	632
690		N-methyl-4-[(1-methyl-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	471.6	628
691		N-methyl-4-({1-methyl-2-[({4-[(4-methylpiperazin-1-yl)methyl]phenyl}carbonyl)amino]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	514.6	627
692		N-methyl-4-{[1-methyl-2-({[4-(morpholin-4-ylmethyl)phenyl]carbonyl}amino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	501.6	627
693		N-methyl-4-{[1-methyl-2-({[4-(piperidin-1-ylmethyl)phenyl]carbonyl}amino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	499.6	627

Example	Structure	Name	MH+	Synthesis as in Example:
694		N-methyl-4-({1-methyl-2-[4-(morpholin-4-ylmethyl)phenyl]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	458.5	628
695		N-methyl-4-({1-methyl-2-[4-(piperidin-1-ylmethyl)phenyl]-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	456.6	628
696		4-({2-[4-({[2-(dimethylamino)ethyl]amino}methyl)phenyl]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	459.6	628
697		4-{[2-(4-{[[2-(dimethylamino)ethyl](methyl)amino]methyl}phenyl)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	473.6	628
698		4-[(4-methylpiperazin-1-yl)methyl]-N-{5-[(4-pyridin-3-ylpyrimidin-2-yl)oxy]-1H-benzimidazol-2-yl}benzamide	521.6	629

Example 699

Step 1. Synthesis of {4-[2-methoxy-4-(methylamino)-5-nitrophenoxy](2-pyridyl)}-N-methylcarboxamide

To a stirred solution of concentrated nitric acid (22eq) was added 2,h-benzo[d]1,3-dioxolane(1eq) at 0-10 °C for 0.5h and stirred for another 0.5h. To this reaction mixture was then added concentrated sulfuric acid (0.06eq) drop-wise at 0-10C° for 0.5h and stirred at 20C° for 0.5h. It was then poured on to crushed ice, and the

separated solid was filtered washed with water and dried to give 5,6-dinitro-2 h-benzol[d]1,3-dioxalane. MS:MH^+ 212

Step 2. Synthesis of methyl(6-nitro(2 h-benzo[3,4-d]1,3-dioxalan-5-yl)amine

To a stirred solution of methyl amine in ether and ethanol (1.5:1) was added 5,6-dinitro-2 h-benzol[d]1,3-dioxalane and stirred at ambient temperature for 24h. The solvent was evaporated under vacuum and the solid was washed with water and dried to give methyl(6-nitro(2 h-benzo[3.4-d]1,3-dioxaln-5-yl))amine. MS: MH^+ 196

Step 3. Synthesis of 2-methoxy-4-(methylamino)-5-nitrophenol

To a stirred solution of methanol was added sodium metal (4.8 eq) slowly at ambient temperature followed by methyl(6-nitro(2 h-benzo[3,4-d]1,3-dioxalan-5-yl))amine (1 eq) and stirred for 2 h. The mixture was then refluxed for 0.5h and diluted with water. After cooling it to ambient temperature the separated solid was filtered and dried to give 2-methoxy-4-(methylamino)-5-nitrophenol as a red solid. MS:MH+ 198

Step 4. Synthesis of {4-[2-methoxy-4-(methylamino)-5-nitrophenoxy](2-pyridyl)}-N-methylcarboxamide

To a stirred solution of 2-methoxy-4-(methylamino)-5-nitrophenol(1eq) in N,N-dimethylacetamide was added potassium-t-butoxide (1.2eq) and continued stirring at ambient temperature untilit solidified. To it was then added (3-chlorophenyl)-N-methylcarboxamide (1eq) and anhydrous potassium carbonate (1eq) and the resulting mixture was heated to 50°C whereby the solid liquified. It was then heated to 110°C for 12 h. After cooling to ambient temperature the solvent was distilled off and the resulting solid was extracted using ethyl acetate in a soxhlet apparatus for 48h. the organic layer was cooled to 0°C , when the product crystallized from the ethyl acetate to give {4-[2-methoxy-4-(methylamino)-5-nitrophenoxy](2-pyridyl)}-N-methylcarboxamide.

MS:MH+ 332

Step 5. Synthesis of 4-{2-[(4-chlrophenyl)amino]-6-methoxy--1-methyl-benzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-6-methoxy-4-(methylamino)phenoxy]pyridine-2-carboxylate(1eq) in methanol was added 4-chlorobenzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-butyl4-(2-{[4-chlorophenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added

trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-chlorophenylamino)-6-methoxy--1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: MH+ = 424.

Step 6. Synthesis of [4-(2-{[4-chlorophenyl)amino-6-methoxy-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

To 4-(2-{[4-chlorophenylamino)-6-methoxy-1-methylbenzimidazol-5-yloxy)-pyridine-2-carboxylic acid(1eq) in tetrahydrofuran was added 2-pyrrolidinylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded [4-(2-{[4-chlorophenyl]amino-6-methoxy-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide. MS: MH+ = 522.

Example 700

Step 1. Synthesis of 4-{2-[(4-bromo-3-methylphenyl)amino]-6-methoxy-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid

To tert-butyl4-[3-amino-6-methoxy-4-(methylamino)phenoxy]pyridine-2-carboxylate(1eq) in methanol was added 4-bromo-3-methylbenzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of tert-butyl4-(2-{[4-bromo-3-methylphenyl]amino)-1-methylbenzimidazol-5-yloxy)pyridine -2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-bromo-3-methylphenylamino)-6-methoxy--1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid was purified by preparative chromatography. MS: MH+ = 482.

Step 2. Synthesis of [4-(2-{[4-bromo-3-methylphenyl)amino-6-methoxy-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide

To 4-(2-{[4-bromo-3-methylpheylamino)-6-methoxy-1-methylbenzimidazol-5-yloxy)pyridine-2-carboxylic acid(1eq) in tetrahydrofuran was added 2-pyrrolidinylethylamine (2eq), HBTU (2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative

chromatography yielded [4-(2-{[4-bromo-3-methylphenyl]amino-6-methoxy-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-(2-pyrrolidinylethyl)carboxamide. MS: MH+ = 579.

Example 701

Step 1. Synthesis of 4-{3-[3-(3-Isopropyl-phenyl)-thioureaido]-4-methylamino-phenoxy}-pyridine-2-carboxylic acid

To tert-butyl4- [3-amino-4- (methylamino) phenoxy] pyridine-2-carboxylate (1eq) in methanol was added 3-isopropylbenzeneisothiocyanate (1eq) and stir at ambient temperature for 16 h. Formation of the corresponding thiourea was followed by LC/MS. To it was then added iodomethane (1eq) and heated to 60°C for 2 h. Formation of 4-{3-[3-(3-Isopropyl-phenyl)-thioureaido]-4-methylamino-phenoxy}-pyridine-2-carboxylate was followed by LC/MS. To it in methylene chloride was added trifluoroacetic acid and stirred at ambient temperature overnight. Resulting 4-(2-{[4-bromo-3-methylphenyl-amino)-1-methylbenzimidazol-5-yloxy) pyridine-2-carboxylic acid was purified by preparative chromatography. MS: MH+ = 437

Step 2. Synthesis of 4-[2-(3-Isopropyl-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylicacid) 2-pyrrolidin-1-yl-ethyl)-amide

To 4-{3-[3-(3-Isopropyl-phenyl)-thioureaido]-4-methylamino-phenoxy}-pyridine-2-carboxylic acid (1eq) in tetrahydrofuran was added 2-pyrrolidinylethylamine (2eq), EDCI (2eq), HOAT (1.2eq) and N,N-diisopropylethylamine (4eq) and stir at ambient temperature for 16 h. The mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was concentrated and preparative chromatography yielded 4-[2-(3-Isopropyl-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylicacid) 2-pyrrolidin-1-yl-ethyl)-amide. MS: MH+ = 499.

Example 702

Step 1. Synthesis of 3-chloro-4-(2-methyl-5-nitrophenyl)pyridine

Nitrogen was bubbled through a solution of 2-bromo-1-methyl-4-nitrobenzene (1eq) in dimethoxyethane and water (3:1) for 0.5h. Bis(diphenylphosphino)ferrocene Palladium(II)chloride (0.05eq) followed by 3-chloro-4-pyridine boronic acid hydrate (1eq) and sodium carbonate (3eq) was added and the mixture was heated to 90°C for 16 h under nitrogen. The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried with sodium

sulfate and concentrated. Purification on silica gel gave 3-chloro-4-(2-methyl-5-nitrophenyl)pyridine. MS: MH+ =248.

Note: The same procedure was used for Suzuki reaction between the halopyridines and the nitrophenylboronic acids.

Boronic acids were synthesized using the following procedure if commercially unavailable.

Step 1a. Synthesis of 2-fluropyridine boronic acid

A flame-dried flask was charged with toluene and tetrahydrofuran (4:1) and then with 4-bromo-2-fluropyridine(1eq) and triisopropylborate (1.2eq) and the flask was cooled to –70°C. Then n-butyllithium (1.2eq) was added dropwise over 0.5h and the mixture was stirred for 0.5h at –70°C. The reaction mixture was then brought to –20°C and 2N hydrochloric acid was added to it. Formation of 2-fluropyridine boronic acid was seen by LC/MS on warming the mixture to ambient temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was dried with sodium sulfate and concentrated to yield 2-fluropyridine boronic acid. MS: MH+ =141.

Step 2. Synthesis of 3-(3-chloro(4-pyridyl)-4-methylphenylamine

To the mixture containing 3-chloro-4-(2-methyl-5-nitrophenyl)pyridine in acetic acid was added Fe dust (5eq) and the resulting mixture was stirred at ambient temperature for 6h. To it was then added saturated sodium carbonate to bring it to neutral pH and extracted with ethyl acetate. The organic layer was washed with brine and dried with sodium sulfate and concentrated and passed through a plug of silica to yield 3-(3-chloro(4-pyridyl))-4-methylphenylamine. MS: MH+ = 218.

Step 3. Synthesis of 3-(3-chlro(4-pyridyl))-4-methylbenzeneisothiocyanate

To 3-(3-chloro(4-pyridyl))-4-methylphenylamine in acetone at 0°C was added sodium bicarbonate (2eq) and thiophosgene (2eq). The mixture was brought to ambient temperature and concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium bicarbonate and sodium sulfate and concentrated to yield 3-(3-chloro(4-pyridyl))-4-methylbenzeneisothiocyanate. MS: MH+ = 260.

Step 4. Synthesis of {4-(2-{[3-(3-chloro(4-pyridyl))-4-methylphenyl]amino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide

To 3-(3-chloro(4-pyridyl))-4-methylbenzeneisothiocyanate(1eq) in methanol was added {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) and the resulting mixture was stirred at ambient temperature for 16 h. LC/MS shows

formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to neutral pH with 1N sodium hydroxide. It was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then titurated with hot methanol to yield {4-(2-{[3-(3-chloro(4-pyridyl))-4-methylphenyl]amino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide. MS: MH+ = 498.

Example 703

1. Synthesis of {4-[2-methoxy-4-(methylamino)-5-nitrophenoxy](2-pyridyl)}-N-methylcarboxamide

To a stirred solution of concentrated nitric acid (22eq) was added 2 h-benzo[d]1,3-dioxolane(1eq) at 0-10 °C for 0.5h and stirred for another 0.5h. To this reaction mixture was then added concentrated sulfuric acid (0.06eq) drop-wise at 0-10C° for 0.5h and stirred at 20C° for 0.5h. It was then poured on to crushed ice, and the separated solid was filtered washed with water and dried to give 5,6-dinitro-2 h-benzol[d]1,3-dioxalane. MS:MH+ 212

Step 2. Synthesis of methyl(6-nitro(2 h-benzo[3,4-d]1,3-dioxalan-5-yl)amine

To a stirred solution of methyl amine in ether and ethanol (1.5:1) was added 5,6-dinitro-2 h-benzol[d]1,3-dioxalane and stirred at ambient temperature for 24h. The solvent was evaporated under vacuum and the solid was washed with water and dried to give methyl(6-nitro(2 h-benzo[3,4-d]1,3-dioxaln-5-yl))amine. MS: MH+ 196

Step 3. Synthesis of 2-methoxy-4-(methylamino)-5-nitrophenol

To a stirred solution of methanol was added sodium metal (4.8 eq) slowly at ambient temperature followed by methyl(6-nitro(2 h-benzo[3,4-d]1,3-dioxalan-5-yl))amine (1 eq) and stirred for 2 h. The mixture was then refluxed for 0.5h and diluted with water. After cooling it to ambient temperature the separated solid was filtered and dried to give 2-methoxy-4-(methylamino)-5-nitrophenol as a red solid. MS:MH+ 198

Step 4. Synthesis of {4-[2-methoxy-4-(methylamino)-5-nitrophenoxy](2-pyridyl)}-N-methylcarboxamide

To a stirred solution of 2-methoxy-4-(methylamino)-5-nitrophenol(1eq) in N,N-dimethylacetamide was added potassium-t-butoxide (1.2eq) and continued stirring at ambient temperature untilit solidified. To it was then added (3-chlorophenyl)-N-

methylcarboxamide (1eq) and anhydrous potassium carbonate (1eq) and the resulting mixture was heated to 50°C whereby the solid liquified. It was then heated to 110°C for 12 h. After cooling to ambient temperature the solvent was distilled off and the resulting solid was extracted using ethyl acetate in a soxhlet apparatus for 48h. The organic layer was cooled to 0°C, when the product crystallized from the ethyl acetate to give {4-[2-methoxy-4-(methylamino)-5-nitrophenoxy](2-pyridyl)}-N-methylcarboxamide.
MS:MH+ 332

Step 5. Synthesis of {4-[3-amino-6-methoxy-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide

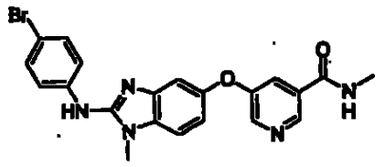
A solution of {4-[2-methoxy-4-(methylamino)-5-nitrophenoxy](2-pyridyl)}-N-methylcarboxamide. In methanol was hydrogenated with 10%Pd/C. The catalyst was filtered off and the solvent was concentrated to yield {4-[3-amino-6-methoxy-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide. MS:MH+: 302.

Step 6. Synthesis of (4-{2-[(4-bromo-3-methylphenyl)amino)]-6-methoxy-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide

To a solution of {4-[3-amino-6-methoxy-4-(methylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide (1eq) in methanol was added 4-bromo-3-methylbenzeneisothiocyanate (1eq) and stirred at 60°C for 2 h. Formation of thiourea was followed by LC/MS. To it was added iodomethane (1eq) and heated to 60°C for 3h. The mixture was concentrated and purified on preparative chromatography to yield (4-{2-[(4-bromo-3-methylphenyl)amino)]-6-methoxy-1-methylbenzimidazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide. MS:MH+ 496.

Example 704

Synthesis of (5-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy)-(3-pyridyl))-N-methylcarboxamide



Step 1. Synthesis of methyl-5-(4-nitrophenoxy)pyridine-3-carboxylate

The mixture containing methyl-5-hydroxypyridine-3-carboxylate (1eq), Potassium bis(trimethylsilyl)amide (1.2eq) was stirred in N,N-dimethylformamide for 2 hours at

room temperature. To this mixture was added 1-fluro-4-nitrobenzene (1.1eq) and Potassium carbonate (1.2eq) and stirred at 80°C for 16 h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried, filtered and concentrated in vacuum to give brown solid. Purification on silica gel methyl-5-(4-nitrophenoxy)pyridine-3-carboxylate. MS: MH+ = 274.

Step 2. Synthesis of methyl5-[4-aminophenoxy]pyridine-3-carboxylate

The mixture containing methyl-5-(4-nitrophenoxy)pyridine-3-carboxylate in methanol with catalytic amount of 10%Pd/C was hydrogenated to yield methyl5-[4-aminophenoxy]pyridine-3-carboxylate. MS: MH+ = 244.

Step 3. Synthesis of methyl-5-[4-(2,2,2-trifluroacetamino)phenoxy]pyridine-3-carboxylate

A solution of methyl-5-[4-aminophenoxy]pyridine-3-carboxylate (1eq) in methylene chloride was treated with trifluoroacetic anhydride (1eq) and stirred for 10 minutes at 0 °C. The mixture was quenched with saturated sodium bicarbonate solution. The organic layer was separated and washed with water , brine, dried and evaporated to yield methyl-5-[4-(2,2,2-trifluroacetamino)phenoxy]pyridine-3-carboxylate. MS: MH+ = 340.

Step 4. Synthesis of methyl5-[3-nitro-4-(2,2,2-trifluroacetylamino)phenoxy]-pyridine-3-carboxylate

To a solution of methyl-5-[4-(2,2,2-trifluroacetamino)phenoxy]pyridine-3-carboxylate in acetic acid and acetic anhydride(1:1) at 0°C was added nitric acid followed by sulfuric acid. Followed the reaction by LC and once complete it was partitioned between ethyl acetate. The organic layer was washed with brine and dried with sodium sulfate and concentrated to yield methyl5-[3-nitro-4-(2,2,2-trifluroacetylamino)phenoxy]-pyridine-3-carboxylate. MS: MH+ = 385.

Step 5. Synthesis of methyl4-[4-(methylamino)-3-nitrophenoxy]pyridine-3-carboxylate

To the solution of the methyl5-[3-nitro-4-(2,2,2-trifluroacetylamino)phenoxy]-pyridine-3-carboxylate (1eq) in a mixture of toluene, acetonitrile and sodium hydroxide solution (50%) was added benzyltrimethylammonium chloride (1eq) and dimethyl sulfate (1.2eq). The biphasic mixture was stirred overnight at room temperature and evaporated. The mixture was taken up in ethyl acetate, washed with water, brine, dried and

evaporated. The crude was purified by column chromatography to afford methyl4-[4-(methylamino)-3-nitrophenoxy]pyridine-3-carboxylate. MS: MH+ = 303.

Step 6. Synthesis of methyl5-[3-amino-4-(methylamino)phenoxy]pyridine-3-carboxylate

The mixture containing methyl4-[4-(amethylamino)-3-nitrophenoxy]pyridine-3-carboxylate was hydrogenated with 10%Pd/C to yield methyl5-[3-amino-4-(methylamino)phenoxy]pyridine-3-carboxylate. MS: MH+ = 273.

Step 7. Synthesis of methyl5-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}pyridine-3-carboxylate

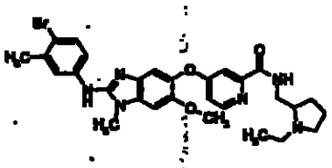
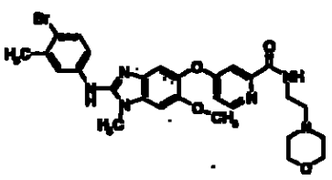
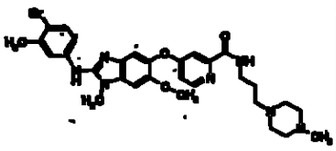
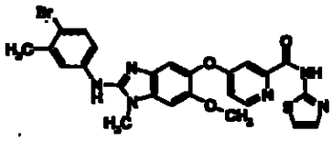
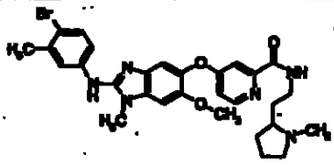
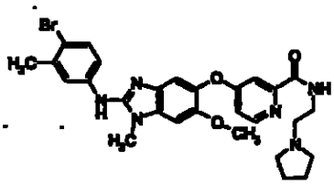
A solution of the methyl5-[3-amino-4-(methylamino)phenoxy]pyridine-3-carboxylate (1eq) in methanol (8 ml) was treated with 4-bromophenylisothiocyanate (1eq) and stirred at 60°C - 65°C for 2 hours. The reaction mixture was cooled down to room temperature and methyl iodide (1eq) was added and stirred overnight at 60°C. The reaction was cooled down to room temperature, evaporated, taken up in ethyl acetate and washed with water and brine, dried, evaporated under reduced pressure. Column chromatography yielded methyl5-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}pyridine-3-carboxylate. MS: MH+ = 452

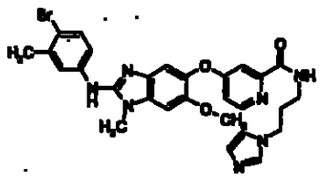
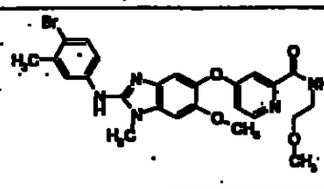
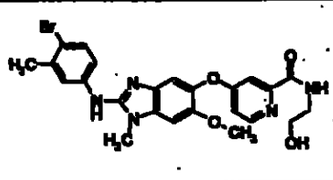
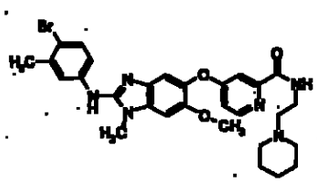
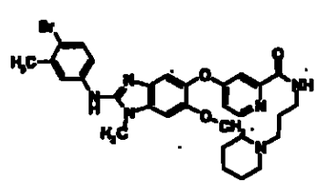
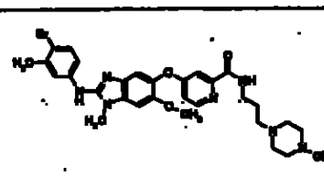
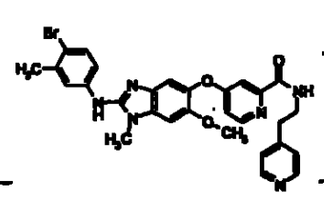
Step 8. Synthesis of (5-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy)-(3-pyridyl))-N-methylcarboxamide

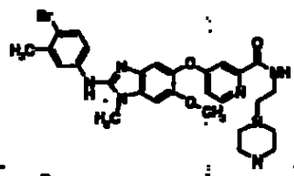
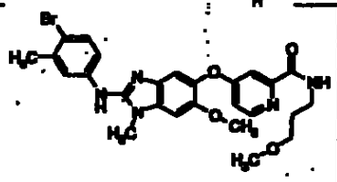
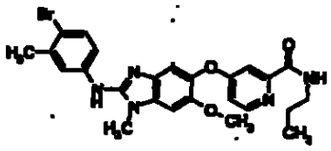
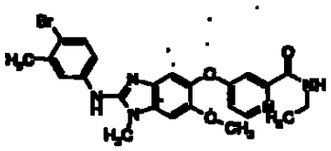
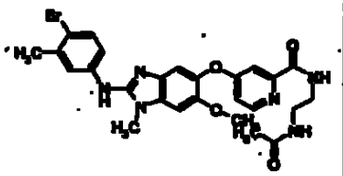
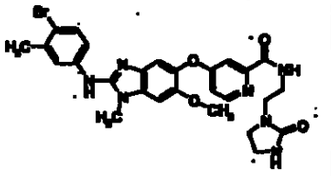
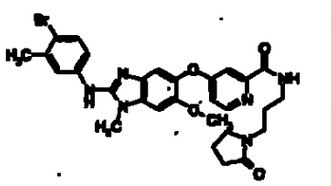
To a solution of methyl5-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}pyridine-3-carboxylate in added methylamine and the resulting mixture was stirred at ambient temperature for 16 h. It was then concentrated and purified by preparative chromatography to yield (5-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy)-(3-pyridyl))-N-methylcarboxamide. MS: MH+ = 452.

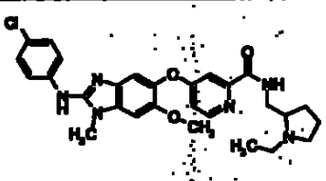
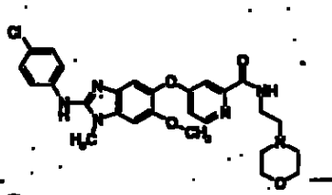
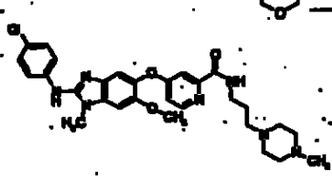
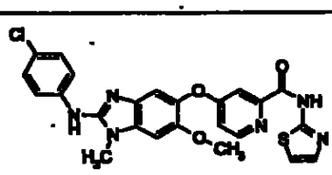
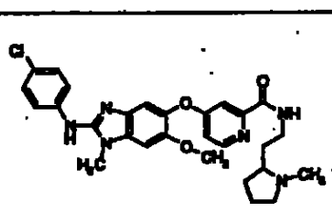
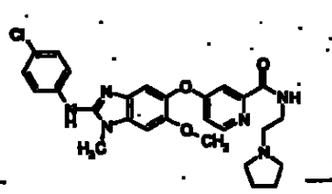
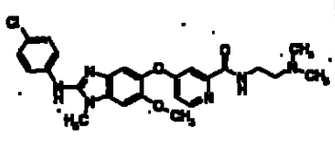
Each of the compounds 705-746, listed in Table 8 were synthesized as indicated in the right hand column by the method described in one of the Examples 699 or 700.

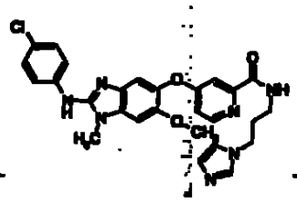
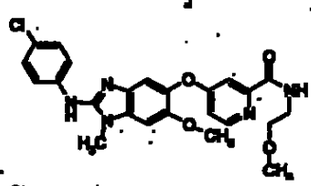
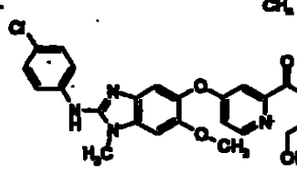
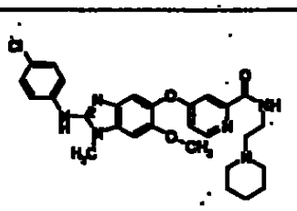
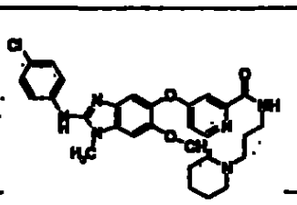
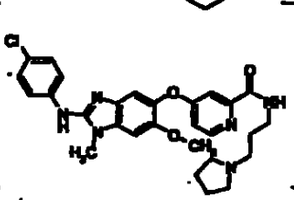
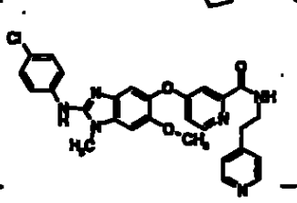
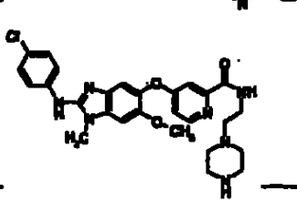
Table 8

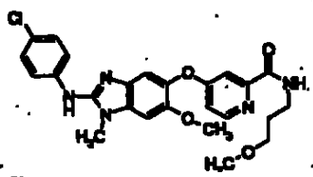
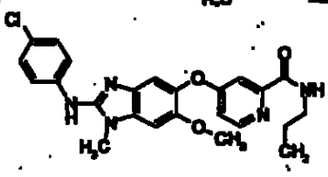
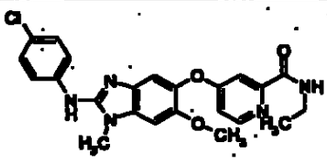
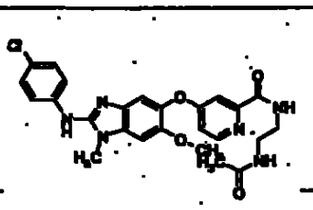
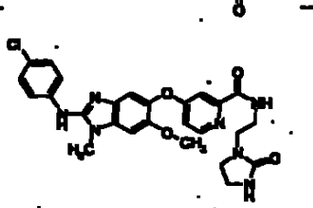
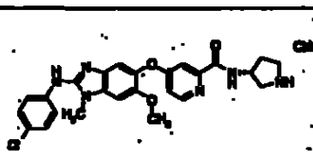
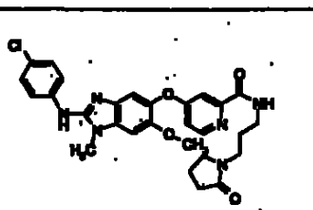
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
705		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[(1-ethyl-pyrrolidin-2-yl)methyl]-pyridine-2-carboxamide	594.5	700
706		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(2-morpholin-4-ylethyl)pyridine-2-carbox-amide	596.5	700
707		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[3-(4-methyl-piperazin-1-yl)propyl]pyridine-2-carboxamide	623.6	700
708		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-1,3-thiazol-2-ylpyridine-2-carboxamide	566.5	700
709		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	594.5	700
710		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(2-pyrrolidin-1-ylethyl)pyridine-2-carbox-amide	580.5	700

Example	Molecular Structure	Name	MH+	Syntheaized as in Example:
711		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[3-(1H-imidazol-1-yl)propyl]pyridine-2-carboxamide	591.5	700
712		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[2-(methyloxy)-ethyl]pyridine-2-carboxamide	541.4	700
713		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(2-hydroxyethyl)-pyridine-2-carboxamide	527.4	700
714		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(2-piperidin-1-ylethyl)pyridine-2-carboxamide	594.5	700
715		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(3-piperidin-1-ylpropyl)pyridine-2-carboxamide	608.5	700
716		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[3-(4-methyl-piperazin-1-yl)propyl]pyridine-2-carboxamide	623.6	700
717		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(2-pyridin-4-yl-ethyl)pyridine-2-carboxamide	588.5	700

Example	Molecular Structure	Name	MH+	Synthesized as in Example:
718		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(2-piperazin-1-yl-ethyl)pyridine-2-carboxamide	595.5	700
719		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[3-(methyloxy)-propyl]pyridine-2-carboxamide	555.4	700
720		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-propylpyridine-2-carboxamide	525.4	700
721		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-ethylpyridine-2-carboxamide	511.4	700
722		N-[2-(acetylamino)ethyl]-4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	568.4	700
723		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[2-(2-oxo-imidazolidin-1-yl)ethyl]-pyridine-2-carboxamide	595.5	700
724		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-[3-(2-oxo-pyrrolidin-1-yl)propyl]-pyridine-2-carboxamide	608.5	700

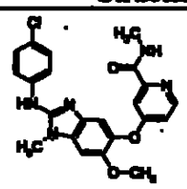
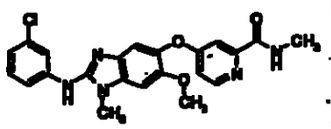
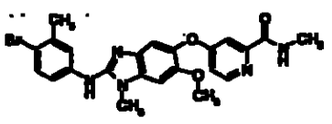
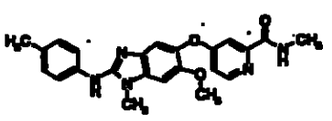
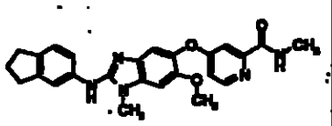
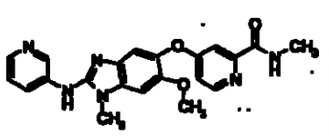
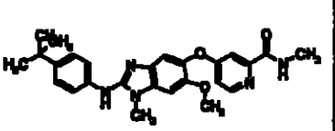
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
725		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-[(1-ethylpyrrolidin-2-yl)methyl]pyridine-2-carbox-amide	536.0	699
726		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-(2-morpholin-4-yl-ethyl)pyridine-2-carboxamide	538.0	699
727		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-[3-(4-methylpiperazin-1-yl)propyl]pyridine-2-carboxamide	565.1	699
728		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-1,3-thiazol-2-yl-pyridine-2-carboxamide	508.0	699
729		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]oxy}-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	536.0	699
730		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-(2-pyrrolidin-1-yl-ethyl)pyridine-2-carboxamide	522.0	699
731		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-[2-(dimethylamino)-ethyl]pyridine-2-carboxamide	496.0	699

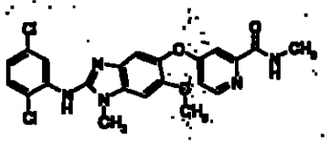
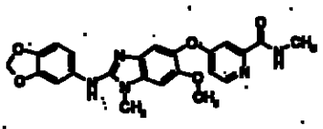
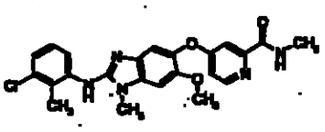
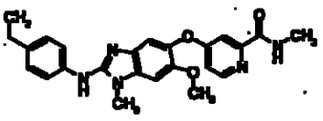
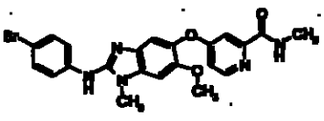
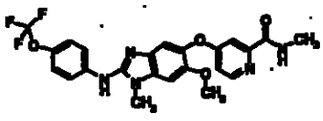
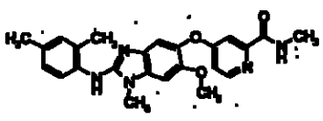
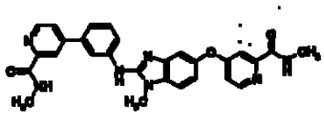
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
732		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-[3-(1H-imidazol-1-yl)-propyl]pyridine-2-carboxamide	533.0	699
733		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-[2-(methyloxy)ethyl]-pyridine-2-carboxamide	482.9	699
734		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-(2-hydroxyethyl)-pyridine-2-carboxamide	468.9	699
735		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-(2-piperidin-1-ylethyl)pyridine-2-carboxamide	536.0	699
736		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-(3-piperidin-1-yl-propyl)pyridine-2-carboxamide	550.1	699
737		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-(3-pyrrolidin-1-yl-propyl)pyridine-2-carboxamide	536.0	699
738		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	530.0	699
739		4-{[2-[(4-chlorophenyl)]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-(2-piperazin-1-ylethyl)pyridine-2-carboxamide	537.0	699

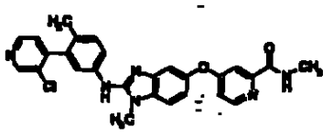
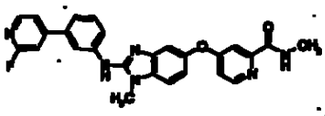
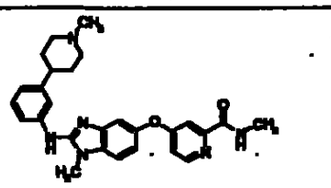
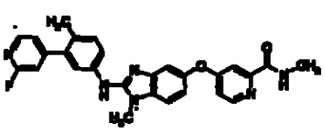
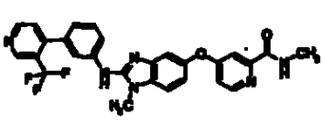
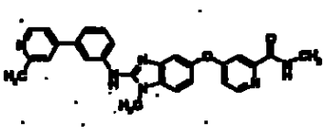
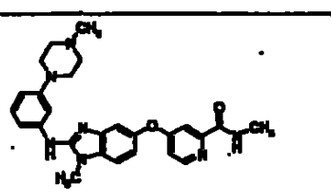
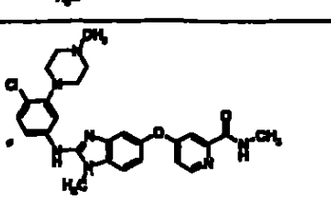
Example	Molecular Structure	Name	MH+	Synthesized as in Example:
740		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]oxy}-N-[3-(methyloxy)-propyl]pyridine-2-carboxamide	497.0	699
741		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-propylpyridine-2-carboxamide	466.9	699
742		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-ethylpyridine-2-carboxamide	452.9	699
743		N-[2-(acetylamino)ethyl]-4-{[2-[(4-chlorophenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	510.0	699
744		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]oxy}-N-[2-(2-oxo-imidazolidin-1-yl)ethyl]-pyridine-2-carboxamide	537.0	699
745		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-[(3R)-pyrrolidin-3-yl]pyridine-2-carboxamide	494.0	699
746		4-{[2-[(4-chlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carbox-amide	550.0	699

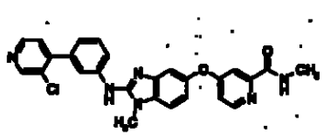
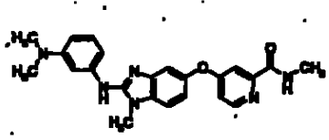
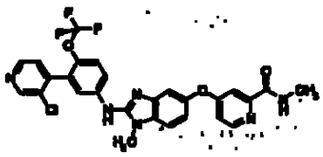
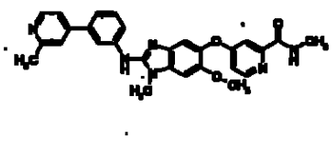
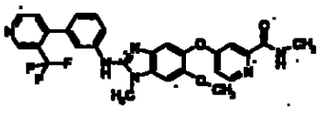
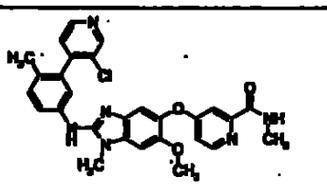
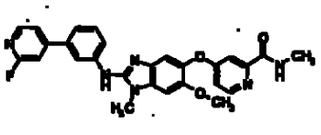
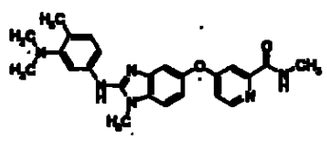
Each of the compounds 747-782, listed in the below table were synthesized as indicated in the right hand column by the method described in one of the Examples 702 or 703 unless indicated otherwise.

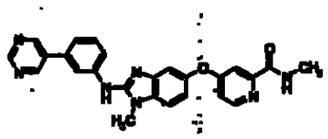
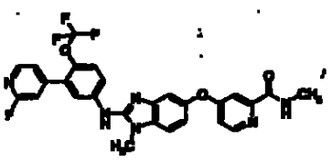
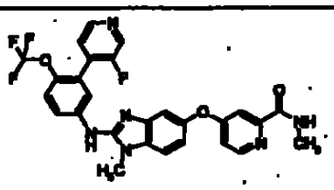
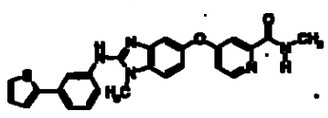
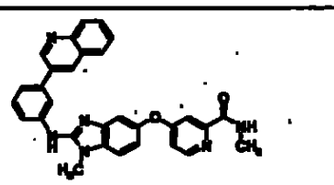
Table 9

Example	Structure	Name	MH+	Synthesized as in Example:
747		4-{[2-[(4-chlorophenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	438.9	703
748		4-{[2-[(3-chlorophenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	438.9	703
749		4-{[2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	497.4	703
750		N-methyl-4-({1-methyl-6-(methyloxy)-2-[(4-methyl-phenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	418.5	703
751		4-{[2-(2,3-dihydro-1H-inden-5-ylamino)-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	444.5	703
752		N-methyl-4-{[1-methyl-6-(methyloxy)-2-(pyridin-3-yl-amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	405.4	703
753		4-{[2-{[4-(1,1-dimethylethyl)-phenyl]amino}-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	460.5	703

Example	Structure	Name	MH+	Synthesized as in Example:
754		4-{[2-[(2,5-dichlorophenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	473.3	703
755		4-{[2-(1,3-benzodioxol-5-ylamino)-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	448.4	703
756		4-{[2-[(3-chloro-2-methyl-phenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	452.9	703
757		4-{[2-[(4-ethylphenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	432.5	703
758		4-{[2-[(4-bromophenyl)amino]-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	483.3	703
759		N-methyl-4-{[1-methyl-6-(methyloxy)-2-({4-[(trifluoro-methyl)oxy]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	488.4	703
760		4-{[2-[(2,4-dimethylphenyl)-amino]-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	432.5	703
761		N-methyl-4-(3-{[1-methyl-5-({2-[(methylamino)carbonyl]-pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}-phenyl)pyridine-2-carboxamide	508.6	703

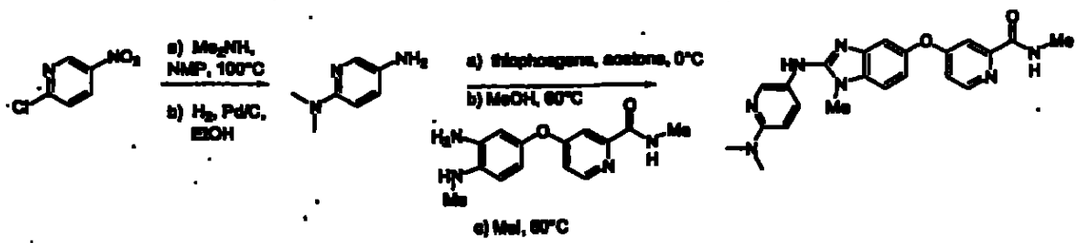
Example	Structure	Name	MH+	Synthesized as in Example:
762		4-[(2-{[3-(3-chloropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	500.0	702
763		4-[(2-{[3-(2-fluoropyridin-4-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	469.5	702
764		N-methyl-4-[(1-methyl-2-{[3-(1-methylpiperidin-4-yl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	471.6	702
765		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	483.5	702
766		N-methyl-4-{[1-methyl-2-({3-[3-(trifluoromethyl)pyridin-4-yl]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	519.5	702
767		N-methyl-4-[(1-methyl-2-{[3-(2-methylpyridin-4-yl)phenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	465.5	702
768		N-methyl-4-[(1-methyl-2-{[3-(4-methylpiperazin-1-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	472.6	702
769		4-[(2-{[4-chloro-3-(4-methyl-piperazin-1-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	507.0	702

Example	Structure	Name	MH+	Synthesized as in Example:
770		4-[(2-{[3-(3-chloropyridin-4-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	485.9	702
771		4-[(2-{[3-(dimethylamino)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	417.5	702
772		4-{[2-({3-(3-chloropyridin-4-yl)-4-[(trifluoromethyl)oxy]-phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	569.9	702
773		N-methyl-4-[(1-methyl-6-(methyloxy)-2-{[3-(2-methyl-pyridin-4-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	495.6	702
774		N-methyl-4-{[1-methyl-6-(methyloxy)-2-({3-[3-(trifluoro-methyl)pyridin-4-yl]phenyl}-amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	549.5	702
775		4-{[2-{[3-(3-chloropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	530.0	702
776		4-{[2-{[3-(2-fluoropyridin-4-yl)phenyl]amino}-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	499.5	702
777		4-[(2-{[3-(dimethylamino)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	431.5	1

Example	Structure	Name	MH+	Synthesized as in Example:
778		N-methyl-4-({1-methyl-2-[(3-pyrimidin-5-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	452.5	702
779		4-{[2-({3-(2-fluoropyridin-4-yl)-4-[(trifluoromethyl)oxy]-phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	553.5	702
780		4-{[2-({3-(3-fluoropyridin-4-yl)-4-[(trifluoromethyl)oxy]-phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	553.5	702
781		N-methyl-4-({1-methyl-2-[(3-thien-2-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	456.5	702
782		N-methyl-4-({1-methyl-2-[(3-quinolin-3-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	501.6	702

Example 783

Synthesis of [4-(2-{[6-(dimethylamino)(3-pyridyl)]amino}-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide

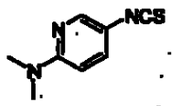


Step 1. Synthesis of 2-(Dimethylamino-5-nitropyridine:

2-Chloro-5-nitropyridine (1.0 eq) and dimethylamine (2 M in EtOH, 4.6 eq) in NMP were heated for 2 h at 100°C. The solution was then poured slowly into H2O. The filtrate that formed was filtered and dried to give 2-(dimethylamino)-5-nitropyridine.

Step 2. Synthesis of 2-(Dimethylamino-5-aminopyridine:

A mixture of 2-(dimethylamino)-5-nitropyridine (1eq) and 5% palladium on carbon (0.3eq) in ethanol was stirred at room temperature and flushed with nitrogen. The reaction vessel was evacuated and purged with hydrogen three times. The reaction mixture was left under an atmosphere of hydrogen overnight. Nitrogen was flushed through the reaction and then the reaction was filtered through a celite pad. The celite pad was washed with excess ethanol before the solvent was removed by evaporation under reduced pressure to afford 2-(dimethylamino)-5-aminopyridine.



Step 3. Synthesis of 2-(Dimethylamino)-5-isothiocynanate pyridine:

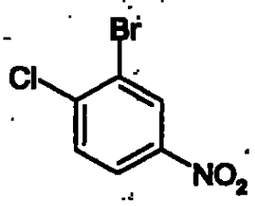
2-(Dimethylamino)-5-aminopyridine (1.0 eq) was taken up in acetone and cooled to 0C. Thiophosgene (1.6 eq) was added dropwise and the reaction was stirred for 30 minutes at 0C before the excess thiophosgene and acetone were removed by evaporation under reduced pressure.

Step 4. Synthesis of [4-(2-{[6-(dimethylamino)(3-pyridyl)]amino}-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-N-methylcarboxamide

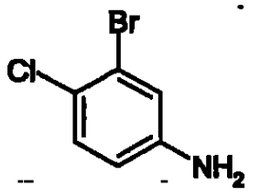
A solution of the {4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-N-methyl-carboxamide (1.1 eq) in methanol was treated with 2-(dimethylamino)-5-isothiocynanate pyridine (1.0 eq) and stirred at 60°C for 2 hours. Methyl iodide (1eq) was added and stirred overnight at 60°C. The reaction was cooled down to room temperature, evaporated and purified by reverse phase HPLC. MS: MH+= 418.3

Example 784

Step 1



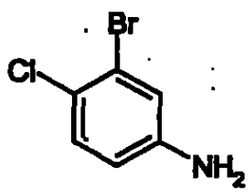
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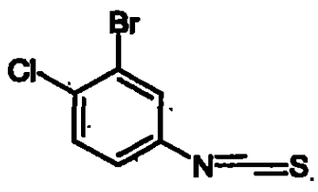
2

A solution of 1 (1eq) and 10% palladium on carbon (0.1eq) in ethyl acetate was stirred at room temperature and flushed with nitrogen. Hydrogen was flushed through the reaction for 2-3 hours or until the reaction was determined to be complete by HPLC. Nitrogen was flushed through the reaction for 15 minutes before the reaction was filtered through a celite pad. The celite pad was washed with excess ethyl acetate and methylene chloride before the combined organic solution was removed by evaporation under reduced pressure to afford the product as a solid 2. MS: MH+ = 207

Step 2



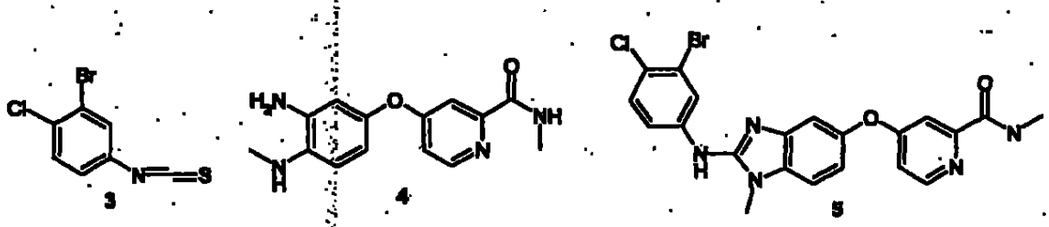
2



3

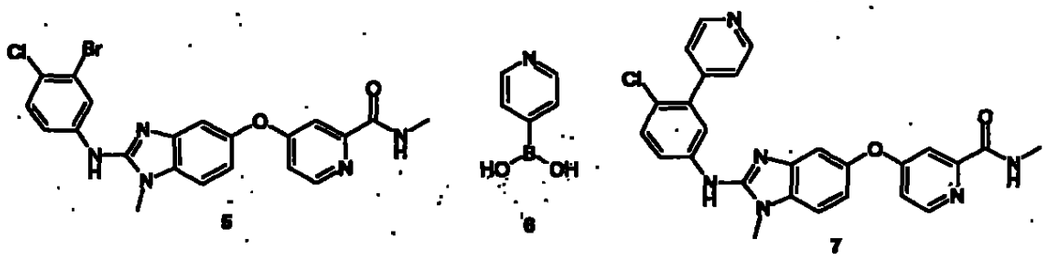
A solution of 2 (1eq) and sodium carbonate (1.5eq) in acetone was stirred under nitrogen in an ice bath. Thiophosgene (1.5eq) was added drop wise over 30 minutes. The reaction was stirred for another 30 minutes in the ice bath before being removed and allowed to warm to RT. The reaction was stirred at RT for 1.5h before the reaction solution was concentrated under vacuum. Toluene was added to the crude product and removed under vacuum to azetrope off any residual thiophoisgene and afford the product 3. MS: MH+ = 249

Step 3



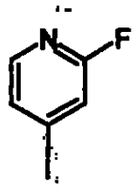
A solution of 3 (1.0eq) and 4 (1.0eq) in MeOH was stirred at RT overnight. Ferric chloride (1.2eq) was added and the resulting reaction mixture was stirred overnight at RT. The reaction mixture was concentrated under vacuum. The crude product was partitioned with EtOAc and water and filtered. The layers were separated and the aqueous phase was neutralized (pH = 7) with saturated Na2CO3 solution. The resulting aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na2SO4), and concentrated to give the desired product 5. MS: MH+ = 487

Step 4

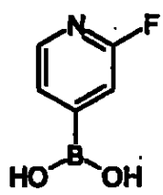


A solution of 5 (1eq), 6 (1eq), and sodium carbonate (1.2eq) in DME/H2O (3:1) was degassed by bubbling argon through the solution for 10 minutes. Pd(II)(dppf)Cl2-MeCl2 (0.1eq) was added to the reaction solution and the reaction was sealed. The reaction was heated at 100°C overnight. The reaction was cooled to RT and ethyl acetate and water were added. The organic layer was separated from the aqueous layer. The aqueous layer was washed once more with ethyl acetate. The organic layers were combined, dried (Na2SO4), and concentrated under vacuum to yield the desired product 7. MS: MH+ = 469

Step 5



8

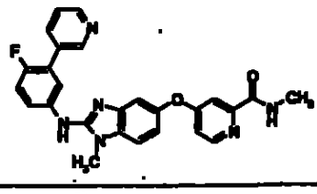
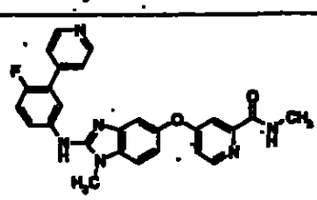


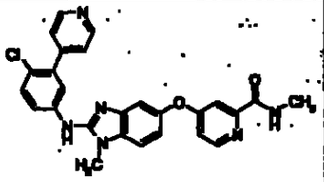
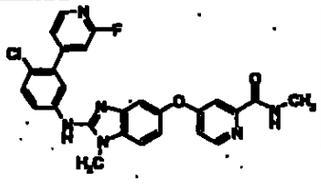
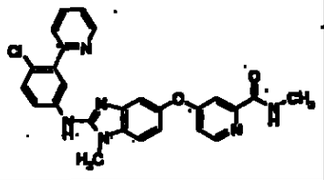
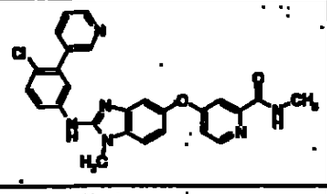
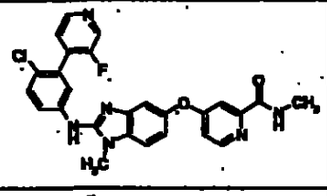
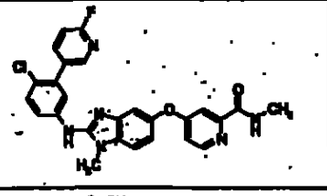
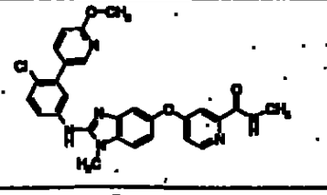
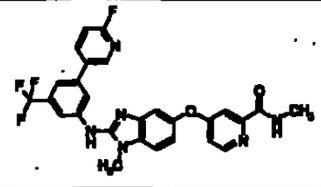
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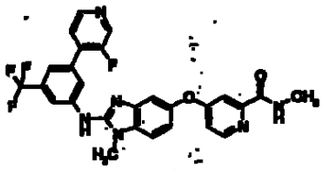
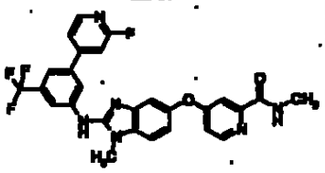
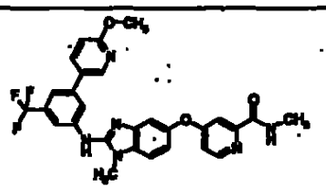
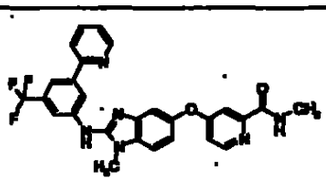
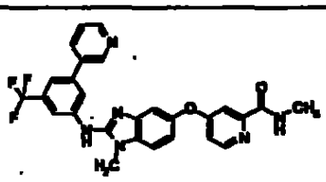
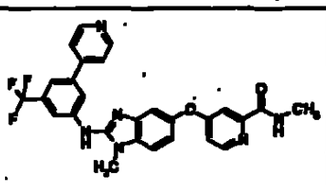
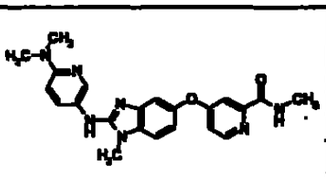
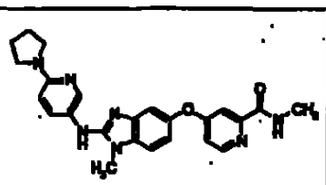
The reaction flask was flame dried and cooled under nitrogen. A solution of 8 (1.0eq) in THF was added to the reaction flask followed by triisopropyl borate (1.2eq). The reaction solution was placed in a dry ice/acetone bath to stir at approximately -72°C. N-butyl lithium (1.5eq, 2.5M solution in hexane) was added drop wise over 40 minutes. The reaction solution was stirred for another 30 minutes in the dry ice/acetone bath. The reaction solution was then transferred to a saturated NaCl/dry ice bath to stir at approx. -25°C and stirred for 20 minutes before 2N HCl (2.0eq) was added. The reaction solution was then removed from the bath to stir and warm to RT. The organic and aqueous layers were separated. The aqueous layer was washed once with ethyl acetate. The organic layers were combined, dried (Na2SO4), and concentrated under vacuum to yield the desired product 9. MS: MH+ = 141

Each of the compounds 785-802, listed in the below table were synthesized as indicated in the right hand column by the method described in one of the Examples 783 or 784.

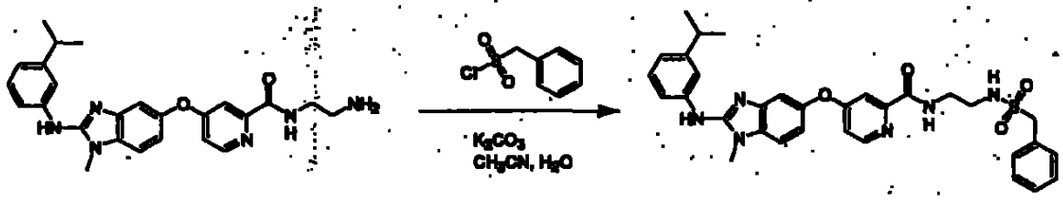
Table 10

Example	Structure	Name	MH^+	Synthesized as in Example:
785		4-({2-[(4-fluoro-3-pyridin-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	469.5	784
786		4-({2-[(4-fluoro-3-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	469.5	784

Example	Structure	Name	MH^+	Synthesized as in Example:
787		4-({2-[(4-chloro-3-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	485.9	784
788		4-[(2-{[4-chloro-3-(2-fluoropyridin-4-yl)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	503.9	784
789		4-({2-[(4-chloro-3-pyridin-2-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	485.9	784
790		4-({2-[(4-chloro-3-pyridin-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	485.9	784
791		4-[(2-{[4-chloro-3-(3-fluoropyridin-4-yl)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	503.9	784
792		4-[(2-{[4-chloro-3-(6-fluoropyridin-3-yl)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	503.9	784
793		4-{[2-({4-chloro-3-[6-(methyloxy)pyridin-3-yl]-phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	516	784
794		4-[(2-{[3-(6-fluoropyridin-3-yl)-5-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	537.5	784

Example	Structure	Name	MH^+	Synthesized as in Example:
795		4-[(2-{[3-(3-fluoropyridin-4-yl)-5-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	537.5	784
796		4-[(2-{[3-(2-fluoropyridin-4-yl)-5-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	537.5	784
797		N-methyl-4-[(1-methyl-2-{[3-[6-(methyloxy)pyridin-3-yl]-5-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	549.5	784
798		N-methyl-4-[(1-methyl-2-{[3-pyridin-2-yl-5-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	519.5	784
799		N-methyl-4-[(1-methyl-2-{[3-pyridin-3-yl-5-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	519.5	784
800		N-methyl-4-[(1-methyl-2-{[3-pyridin-4-yl-5-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	519.5	784
801		4-[(2-{[6-(dimethylamino)-pyridin-3-yl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	418.5	783
802		N-methyl-4-({1-methyl-2-[(6-pyrrolidin-1-ylpyridin-3-yl)-amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	444.5	783

Example 803

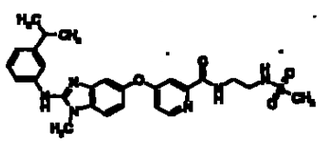
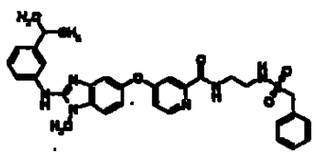


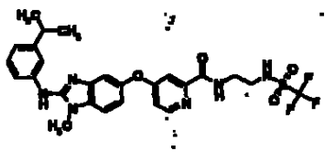
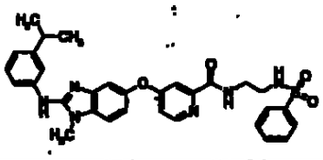
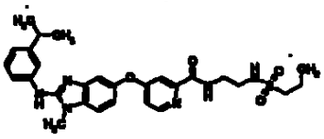
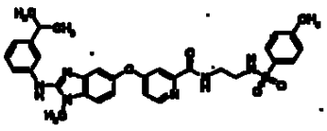
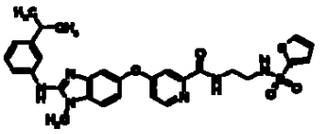
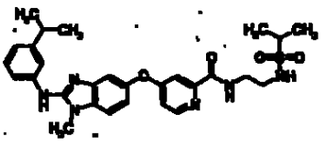
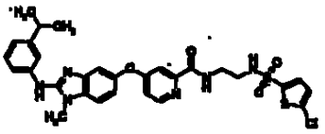
Step 1. 4-[2-(3-Isopropyl-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid (2-phenylmethanesulfonylamino-ethyl)-amide

To a mixture containing 4-[2-(3-Isopropyl-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid (2-amino-ethyl)-amide (1eq) (prepared using previously described example 3), K2CO3 (5eq), (0.2 M in a 5:1 mixture of acetonitrile and water) were added α-toluenesulfonyl chloride (1 eq) via syringe. The resulting heterogeneous mixture was allowed to stir for 1 hour at room temperature. The mixture was then diluted with water and extracted with dichloromethane. The organics were washed with water and a saturated solution of sodium chloride, dried with sodium sulfate and concentrated in vacuo to viscous oil. Purification by chromatography yielded 4-[2-(3-Isopropyl-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid (2-phenylmethanesulfonylamino-ethyl)-amide. MS: MH+ 599

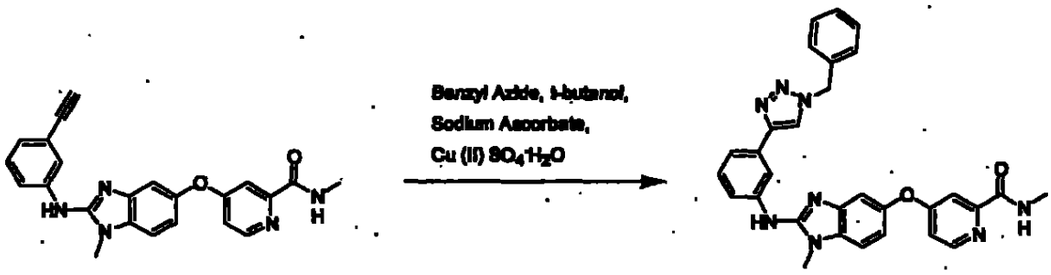
The compounds shown in the following Table (Examples 804-812) were prepared from following the procedure described for Example 803.

Table 11

Example	Structure	Name	MH+
804		4-[(1-methyl-2-{[3-(1-methyl-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-{2-[(methylsulfonyl)amino]-ethyl}pyridine-2-carboxamide	523.6
805		4-[(1-methyl-2-{[3-(1-methyl-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-{[(phenylmethyl)sulfonyl]-amino}ethyl)pyridine-2-carboxamide	599.7

Example	Structure	Name	MH+
806		4-[(1-methyl-2-{[3-(1-methylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-{[(trifluoromethyl)sulfonyl]amino}ethyl)pyridine-2-carboxamide	577.6
807		4-[(1-methyl-2-{[3-(1-methylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-{2-[(phenylsulfonyl)amino]ethyl}-pyridine-2-carboxamide	585.7
808		4-[(1-methyl-2-{[3-(1-methylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-{2-[(propylsulfonyl)amino]-ethyl}pyridine-2-carboxamide	551.7
809		4-[(1-methyl-2-{[3-(1-methylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-{[(4-methylphenyl)sulfonyl]-amino}ethyl)pyridine-2-carboxamide	599.7
810		4-[(1-methyl-2-{[3-(1-methylethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-{2-[(thien-2-ylsulfonyl)amino]-ethyl}pyridine-2-carboxamide	591.7
811		N-(2-{[(1-methylethyl)-sulfonyl]amino}ethyl)-4-[(1-methyl-2-{[3-(1-methylethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	551.7
812		N-(2-{[(5-chlorothien-2-yl)-sulfonyl]amino}ethyl)-4-[(1-methyl-2-{[3-(1-methylethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	626.2

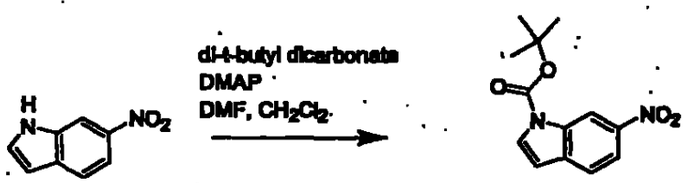
Example 813



Step 1. 4-{2-(3-(1-Benzyl-1H- [1,2,3] triazol-4-yl)-phenyl amino]-1-methyl-1H-benzoimidazol-5-yloxy}-pyridine-2-carboxylic acid methyl amide

To a mixture of 4-[2-(3-Ethynl-phenylamino)-1-methyl-1H-benzoimidazol-5-yl-oxy]-pyridine-2-carboxylic acid methylamide (1eq)(prepared using previously described example 2), benzyl azide (1eq) in t-butanol (0.1M) was added sodium ascorbate (0.05eq), and copper (II) sulfate pentahydrate (0.01eq). The resulting mixture was allowed to stir for 1 hour at room temperature. The mixture was then diluted with water and the solid collect via suction filtration. MS: MH+ 531

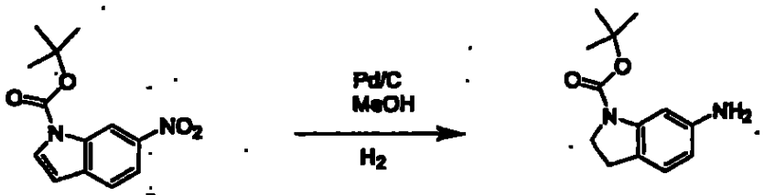
Example 814



Step 1. Synthesis of 6-Nitro-indole-1-carboxylic acid t-butyl ester

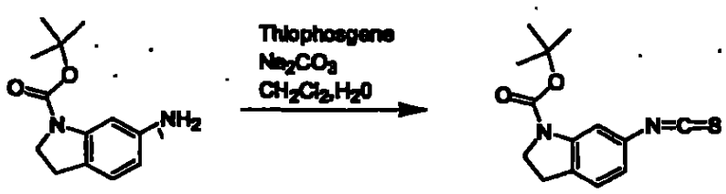
To a stirring solution of 6-nitroindole (1eq) in dichloromethane (0.3M) and DMF (3.1M), was added di-t-butyl dicarbonate (2eq) followed by the addition of 4-(dimethyl amino) pyridine (1eq). Resulting solution was allowed to stir overnight at room temperature. The dichloromethane was then removed on a rotovap and remaining solution diluted with water and extracted with ethyl acetate. Organics were washed with 10% citric acid solution, saturated solution of sodium chloride, saturated solution of sodium bicarbonate, saturated solution of sodium chloride and dried with sodium sulfate. Ethyl acetate was then removed in vacuo. Ethyl ether was then added and a brown solid

was collected by suction filtration to yield 6-Nitro-indole-1-carboxylic acid t-butyl ester. MS: MH+ 263



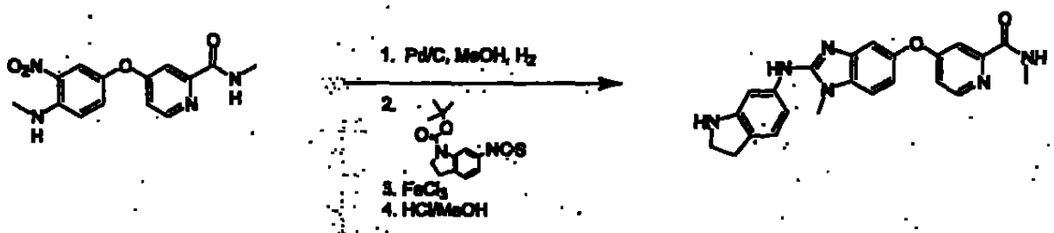
Step 2. Synthesis of 6-Amino-2, 3-dihdro-indole-1-carboxylic acid t-butyl ester

6-Nitro-indole-1-carboxylic acid t-butyl ester (1eq) was dissolved in methanol (0.1M), to this solution was added palladium on carbon (0.1eq) in methanol under nitrogen. A hydrogen atmosphere was then inserted and resulting mixture allowed to stir for 3 hours at room temperature. The reaction mixture was then filtered through celite and solvent removed in vacuo to afford 6-Amino-2, 3-dihdro-indole-1-carboxylic acid t-butyl ester as a white solid. MS: MH+ 235



Step 3. Synthesis of 6-Isothiocyanate-2, 3-dihydro-indole-1-carboxylic acid t-butyl ester

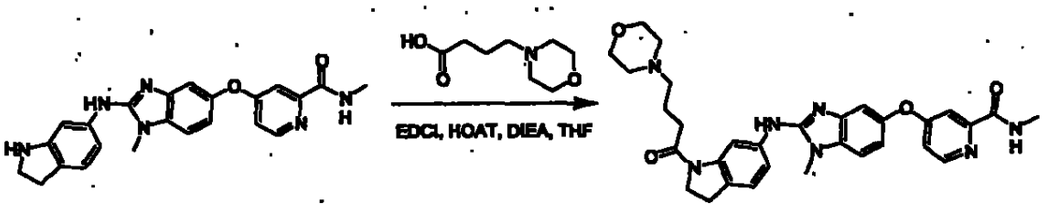
Thiophosgene (1.1 eq) was added to a stirred suspension of 6-Amino-2, 3-dihdro-indole-1-carboxylic acid t-butyl ester (1eq), sodium carbonate (10eq), and dichloromethane: water 3:1 by volume at 0oC. The resulting mixture was allowed to stir for 2 hours at 0oC. The mixture was diluted with water and organics separated and washed with water, saturated solution of sodium chloride and dried with sodium sulfate, solvent removed in vacuo to afford 6-Isothiocyanate-2, 3-dihydro-indole-1-carboxylic acid t-butyl ester as orange oil.



Step 4. Synthesis of 4-[2-(2,3-Dihydro-1H-indol-6-ylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid methylamide.

To a solution of 4-(4-Methylamino3-nitro-phenoxy)-pyridine-2-carboxylic acid methylamide (1eq) in methanol (0.1M) was added palladium on carbon (0.1eq) under nitrogen. The atmosphere was exchanged for hydrogen (1 atm) and the resulting suspension allowed to stir for 2 hours at room temperature. The mixture was filtered through celite and added to 6-Isothiocyanate-2, 3-dihydro-indole-1-carboxylic acid t-butyl ester (1 eq). The resulting solution was allowed to stir overnight. Iron (III) chloride(2 eq) in methanol was added and the solution turns deep red in color. This solution was allowed to stir for 3 hours at room temperature. Methanol was then removed in vacuo; the resulting oil was diluted with water and extracted with dichloromethane. Organics were washed with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution and dried with sodium sulfate. Solvent was removed in vacuo. To the resulting oil was added toluene and heated to reflux, solution was cooled to room temperature and a solid was collected after 3 days by suction filtration to afford 4-[2-(2,3-Dihydro-1H-indol-6-ylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid methylamide. MS: MH+ 415

Example 815

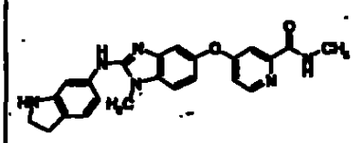
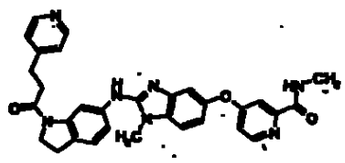
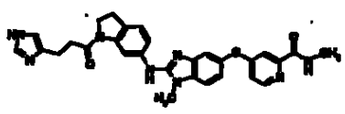
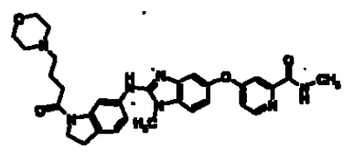


Step 1. Synthesis of 4-{1-Methyl-2- [1-(4-morpholin-4-yl-butylryl)-2,3-dihydro-1H-indol-6-ylamino]-1H-benzoimidazol-5-yloxy}-pyridine-2-carboxylic acid methyl-amide

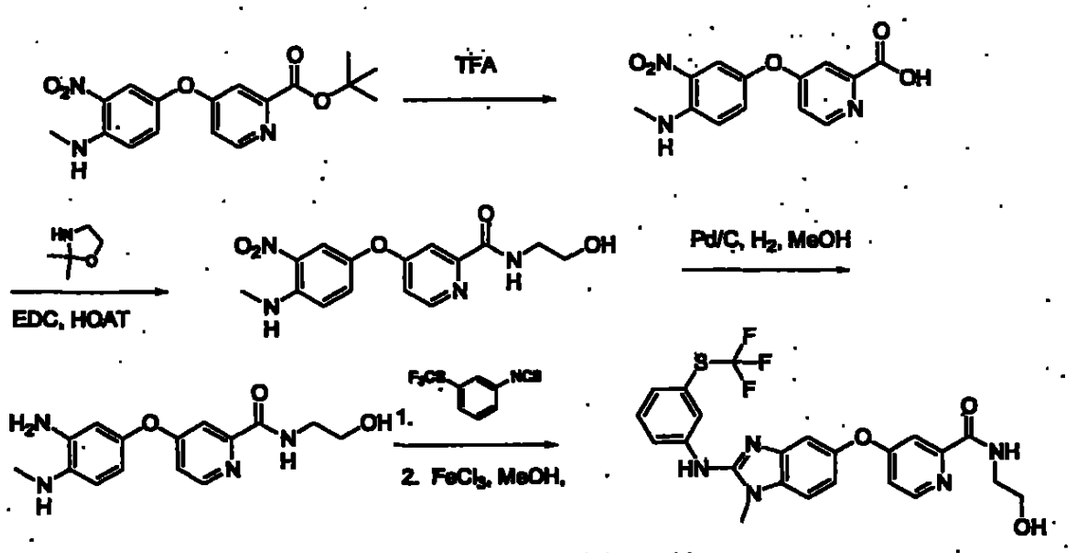
To mixture containing 4-[2-(2,3-Dihydro-1H-indol-6-ylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid methylamide (1eq)(previously prepared using example 1), EDCI (2eq), HOAT (1.2eq), DIEA (4eq) was added THF. The mixture was allowed to stir overnight at room temperature under nitrogen. The mixture was then diluted with water, extracted with ethyl acetate. Organics were washed with water, then saturated solution of sodium chloride and dried with sodium sulfate, filtered and the solvent was removed in vacuo. Purification by chromatography yielded 4-{1-Methyl-2- [1-(4-morpholin-4-yl-butyiryl)-2,3-dihydro-1H-indol-6-ylamino]-1H-benzoimidazol-5-yloxy}-pyridine-2-carboxylic acid methylamide. MS: MH+ 570

The compounds shown in the following table (Examples 816-819) were prepared from following the procedure described for Example 815.

Table 12

Example	Structure	Name	MH+
816		4-{[2-(2,3-dihydro-1H-indol-6-ylamino)-1-methyl-1H-benz-imidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	415.5
817		N-methyl-4-[(1-methyl-2-{[1-(3-pyridin-4-ylpropanoyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	548.6
818		4-{[2-({1-[3-(1H-imidazol-4-yl)-propanoyl]-2,3-dihydro-1H-indol-6-yl}amino)-1-methyl-1H-benz-imidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	537.6
819		N-methyl-4-[(1-methyl-2-{[1-(4-morpholin-4-ylbutanoyl)-2,3-dihydro-1H-indol-6-yl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	570.7

Example 820



Step 1. Synthesis of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carboxylic acid:

A stirring solution of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carboxylic acid tert-butyl ester in trifluoroacetic acid was treated with two drops of water at room temperature for 3-4 hours or when the reaction was determined to be complete by HPLC. The reaction was evaporated under reduced pressure to afford the product as a red-orange oil. Addition of ethyl ether, sonication, and filtration captures the product as a light pink solid. LCMS m/z 290.1 (MH+), tR = 1.71 min.

Step 2. Synthesis of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide:

To a suspension of the 4-(4-methylamino-3-nitro-phenoxy)-pyridine-2-carboxylic acid (1eq) in dry THF, EDC-HCl (1.2eq), HOAT (1.2eq), and diisopropylethylamine (3 eq) were added. The suspension was stirred for 10 minutes whereupon 2,2-dimethyl-oxazolidine (1.1eq) was added and the solution is allowed to stir overnight. The mixture was then diluted with ethyl acetate and washed with water. The aqueous layer was washed with ethyl acetate, the organic layers combined, dried over MgSO4, filtered, and concentrated. LCMS m/z 333.2 (MH+), tR = 2.1 min.

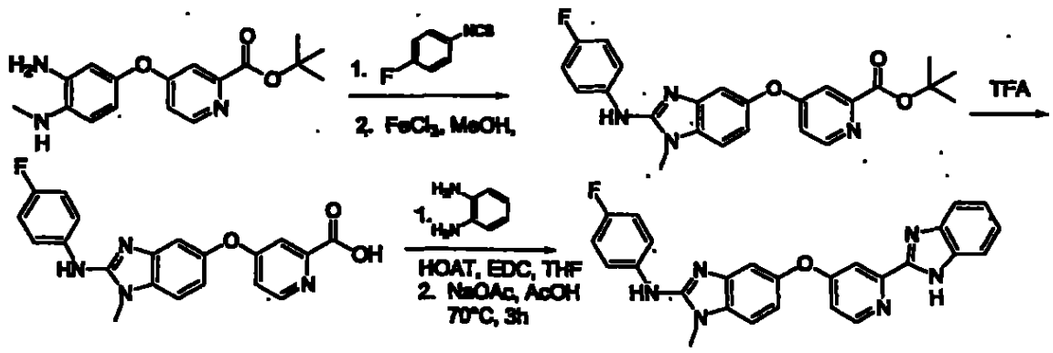
Step 3. 4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide:

A solution of 4-(4-methylamino-3-nitro-phenoxy)-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide (1eq) and 10% palladium on carbon (0.1eq) in methanol was stirred at room temperature and flushed with nitrogen. Hydrogen was flushed through the reaction for 1-2 hours or until the reaction was determined to be complete by HPLC. Nitrogen was flushed through the reaction for 15 minutes before the reaction was filtered through a celite pad. The celite pad was washed with excess methanol before it was all removed by evaporation under reduced pressure to afford the product as a light yellow solid. LCMS m/z 303.2 (MH+), tR = 1.5 min.

Step 4. 4-[1-Methyl-2-(3-trifluoromethylsulfanyl-phenylamino)-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide:

A flask was charged with 3-(trifluoromethylthio)phenylisothiocyanate (1eq), 4-(3-amino-4-methylamino-phenoxy)-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide (1eq), and MeOH. The reaction was maintained at rt overnight. Ferric chloride, (1.5eq) was added and the resulting red reaction mixture was stirred overnight. The reaction was partitioned with EtOAc and water, and filtered through Celite. The layers were separated and the aqueous phase was neutralized with saturated Na2CO3 solution. The resulting aqueous phase was extracted with EtOAc and the mixture was filtered through Celite. The phases were separated and the aqueous phase was again extracted and filtered. The combined organic layers were washed with brine, dried (MgSO4), filtered, and concentrated to give a brown solid. The crude residue was purified by reverse phase HPLC. LCMS m/z 504.1 (MH+), tR = 3.7 min.

Example 821



Step 1. Synthesis of 4-[2-(4-Fluoro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid tert-butyl ester:

A round bottom flask was charged with 4-fluorophenylisothiocyanate (1eq), 4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carboxylic acid tert-butyl ester (1eq), and MeOH. The reaction was maintained stirring at room temperature overnight. Ferric chloride, (1.5eq) was added and the resulting mixture was stirred overnight. The reaction was partitioned with EtOAc and water, and filtered through Celite. The layers were separated and the aqueous phase was neutralized with saturated Na2CO3 solution. The resulting aqueous phase was extracted with EtOAc and the mixture was filtered through Celite. The phases were separated and the aqueous phase was again extracted and filtered. The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated to give a brown solid. The crude residue was purified by trituration in hot toluene to furnish the desired product. LCMS m/z 435.6 (MH+), tR = 2.12 min.

Step 2. Synthesis of 4-[2-(4-Fluoro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid:

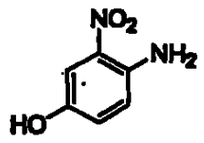
A stirring solution of 4-[2-(4-Fluoro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid tert-butyl ester in trifluoroacetic acid was treated with two drops of water at room temperature for 3-4 hours or when the reaction was determined to be complete by HPLC. The reaction was evaporated under reduced pressure and then ether was added to the residue, which was then sonicated for 30 minutes. Filtration and washing with ether yields the desired acid in quantitative yield. LCMS m/z 379.4 (MH+), tR = 1.74 min.

Step3. Synthesis of {5-[2-(1H-Benzoimidazol-2-yl)-pyridin-4-yloxy]-1-methyl-1H-benzoimidazol-2-yl}-(4-fluoro-phenyl)-amine:

To a suspension of 4-[2-(4-Fluoro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid (1eq) in dry THF, EDC-HCl (1.2eq), HOAT (1.2eq), and diisopropylethylamine (3 eq) were added. The suspension was stirred for 10 minutes whereupon phenylenediamine (1.1 eq) was added and the solution is allowed to stir overnight. The mixture was then diluted with ethyl acetate and washed with water. The aqueous layer was washed with ethyl acetate, the organic layers combined, dried over MgSO4, filtered, and concentrated. Acetic acid was added to the residue followed by sodium acetate (1.1 eq). The mixture was heated for 3 hours at 70°C, whereupon the solution is concentrated and the residue purified by reverse phase HPLC to afford the desired product. LCMS m/z 451.5 (MH+), tR = 1.92 min.

SYNTHESIS OF SIDE CHAINS

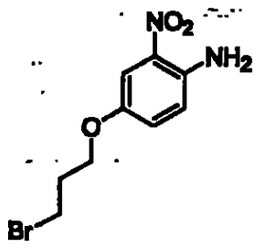
Ether Substituted phenylenediamines:



1



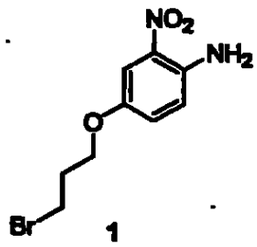
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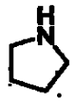
3

4-(3-Bromopropoxy)-2-nitrophenylamine:

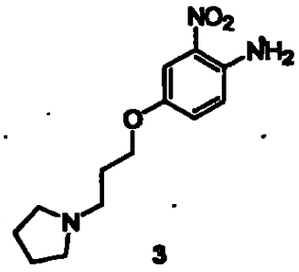
A flask is charged with 4-amino-3-nitrophenol 1 (1 eq), K_2CO_3 (2 eq), and 2-butanone. 1,3-dibromopropane 2 (1.5 eq) is added and the mixture is heated at 80°C for 18 hours. After cooling, the mixture is filtered concentrated and water is added. The solution is then extracted with CH_2Cl_2 (x3), the organic layer concentrated, and the solid recovered washed with pentane to yield the desired product 3. LCMS *m/z* 275.1 (MH+), R_t 2.74 minutes.



1



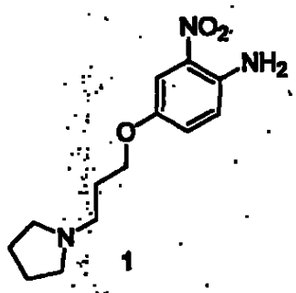
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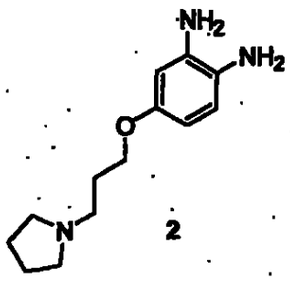
3

2-Nitro-4-(3-pyrrolidinylpropoxy)phenylamine:

4-(3-bromopropoxy)-2-nitrophenylamine 1 (1 eq) was heated to 70°C with pyrrolidine 2 (5 eq) in MeCN with Cs_2CO_3 (2 eq) and Bu_4NI (0.1 eq) for 48 hours. The reaction mixture was cooled, filtered, and concentrated. The residue is dissolved in CH_2Cl_2, and washed with water. The organic layer is concentrated yielding the desired product 3. LCMS *m/z* 266.2 (MH+), R_t 1.51 minutes.



1

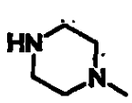


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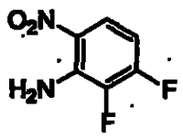
4-(3-Pyrrolidinylpropoxy)benzene-1,2-diamine:

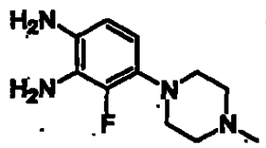
To a solution 2-Nitro-4-(3-pyrrolidinylpropoxy)phenylamine 1 in EtOH, Pd/C (0.1eq) is added. The reaction vessel is repeatedly purged (x3) with nitrogen, and then stirred under a hydrogen atmosphere for 18 h. The product is filtered through a Celite plug, and the plug washed with 25 mL of EtOH, to yield 2. LCMS 236.2 R, 0.94 min.

3-Fluoro-4-amino substituted phenylenediamines:



1





2

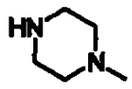
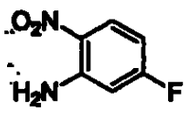
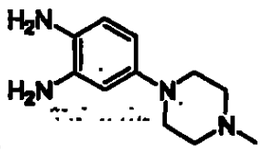
1. Synthesis of 2-Fluoro-3-(4-methyl-piperazin-1-yl)-6-nitro-phenylamine.

A solution of N-methylpiperazine (1.0 eq), NMP, triethylamine (3.0 eq) and 5,6-difluoro-2-nitroaniline (1.0 eq) were heated at 90oC for 1 hour. The reaction was allowed to cool to room temperature and then poured into water and let stand for 1 hour. The resulting solid was collected and dried and utilized without further purification. MH+ = 255.3

2. Synthesis of 3-Fluoro-4-(4-methyl-piperazin-1-yl)-benzene-1,2-diamine.

To a solution Synthesis of 2-fluoro-3-(4-methyl-piperazin-1-yl)-6-nitro-phenylamine in EtOH, Pd/C (0.1eq) is added. The reaction vessel is repeatedly purged (x3) with nitrogen, and then stirred under a hydrogen atmosphere for 18 h. The product is filtered through a Celite plug, the plug washed with 25 mL of EtOH, to yield the desired diamine. LCMS 225.3 Rt 0.45 min.

4-Amino substituted phenylenediamines (a):

1 2

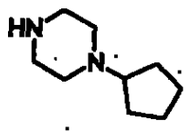
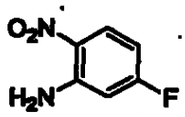
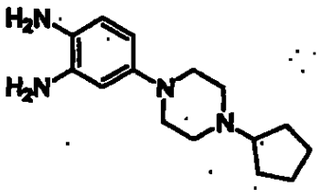
Synthesis of 5-(4-Methyl-piperazin-1-yl)-2-nitro-phenylamine

A solution of N-methylpiperazine (1.0 eq), NMP, triethylamine (3.0 eq) and 5-fluoro-2-nitrophenylamine (1.0 eq) were heated at 90°C for 1 hours. The reaction was allowed to cool to room temperature and then poured into water and let stand for 12 hours. The resulting solid was collected and dried and utilized without further purification. MH+ = 237.3.

Synthesis of 4-(4-Methyl-piperazin-1-yl)-benzene-1,2-diamine:

To a solution 5-(4-Methyl-piperazin-1-yl)-2-nitro-phenylamine in EtOH, Pd/C (0.1eq) is added. The reaction vessel is repeatedly purged (x3) with nitrogen, then stirred under a hydrogen atmosphere for 18 h. The product is filtered through a Celite plug, the plug washed with 25 mL of EtOH, to yield the desired diamine. LCMS 207.3 Rt 0.25 min.

4-Amino substituted phenylenediamines (b):

1 2

Synthesis of 5-(4-Cyclopentyl-piperazin-1-yl)-2-nitro-phenylamine

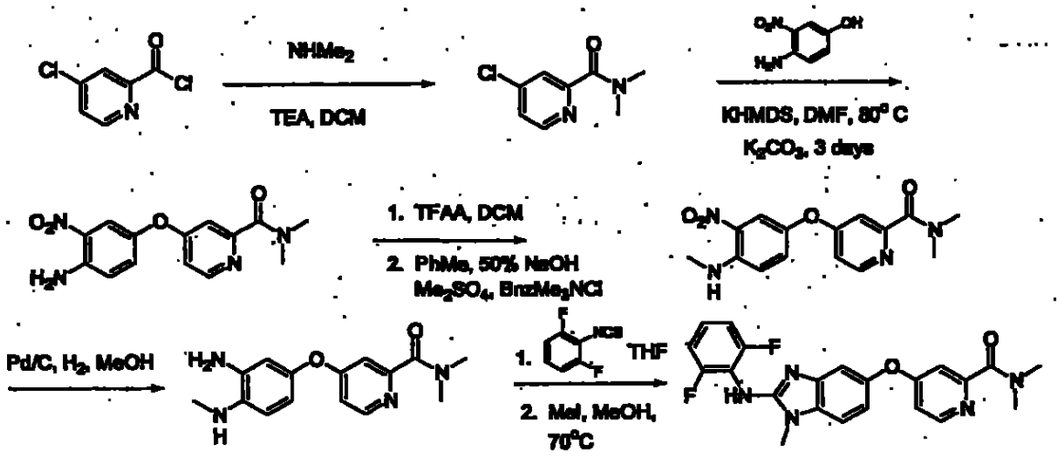
1. A solution of N-cyclopentylpiperazine (1.0 eq), NMP, triethylamine (3.0 eq) and 5-fluoro-2-nitrophenylamine (1.0 eq) were heated at 90°C for 1 hours. The reaction was allowed to cool to room temperature and then poured into water and let stand for 12

hours. The resulting solid was collected and dried and utilized without further purification. MH+ = 291.4.

2. Synthesis of 4-(4-Cyclopentyl-piperazin-1-yl)-benzene-1,2-diamine:

To a solution 5-(4-Cyclopentyl-piperazin-1-yl)-2-nitro-phenylamine in EtOH, Pd/C (0.1eq) is added. The reaction vessel is repeatedly purged (x3) with nitrogen, then stirred under a hydrogen atmosphere for 18 h. The product is filtered through a Celite plug, the plug washed with 25 mL of EtOH, to yield the desired diamine. MH+ = 261.3.

Example 822



Step 1. Synthesis of 4-Chloro-pyridine-2-carboxylic acid dimethylamide:

A solution of 4-chloro-pyridine-2-carbonyl chloride (1eq) in dichloromethane was cooled to 0°C, whereupon triethylamine (2eq) was added followed by dimethylamine (2eq, 2M solution in THF). The solution was allowed to warm to room temperature and let stir overnight. It was then washed with 1M NaOH. The separated organic layer is dried over MgSO4, filtered, and concentrated to yield the desired product. HPLC, 1.82 min; MS: MH+ = 185.6

Step 2. Synthesis of 4-(4-Amino-3-nitro-phenoxy)-pyridine-2-carboxylic acid dimethylamide:

A mixture containing 4-amino-3-nitrophenol (1eq) and potassium bis(trimethylsilyl)amide (2eq) was stirred in dimethylformamide for 2 hours at room temperature. To this mixture was added 4-Chloro-pyridine-2-carboxylic acid dimethylamide (1eq) and potassium carbonate (1.2eq) and then it was stirred at 90oC for 3 days. The reaction mixture was then concentrated before partitioning between ethyl

acetate and water. The organic layer was separated, washed with brine, dried, filtered and concentrated in vacuum to give brown solid. Purification by flash chromatography with ethyl acetate and hexane (1:1) gave the desired product as a yellow syrup. HPLC, 1.69 min; MS: MH+ = 303.1.

Step 3. Synthesis of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carboxylic acid dimethylamide:

A solution of 4-(4-Amino-3-nitro-phenoxy)-pyridine-2-carboxylic acid dimethylamide (1eq) in methylene chloride was treated with trifluoroacetic anhydride (1eq) and stirred for 10 minutes at 0°C. The mixture was quenched with satd. NaHCO3 solution. The organic layer was separated and washed with water, brine, dried, filtered and evaporated. MS: MH+=399.0

To the solution of the trifluoroacetamide (1eq) in a mixture of toluene, acetonitrile and sodium hydroxide solution (50%) was added benzyltrimethylammonium chloride (1eq) and dimethyl sulfate (1.2eq). The biphasic mixture was stirred overnight at room temperature. The mixture was taken up in ethyl acetate, washed with water, brine, dried and evaporated. The crude was purified by flash chromatography eluting with 5% methanol in dichloromethane to afford the desired product. HPLC, 2.14 min; MS: MH+ = 317.3

Step 4. Synthesis of 4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carboxylic acid dimethylamide:

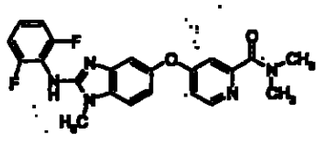
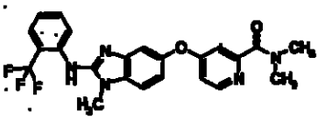
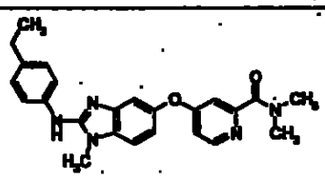
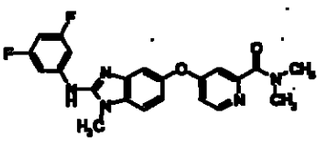
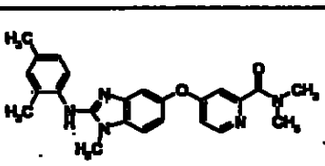
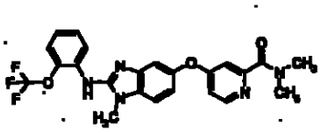
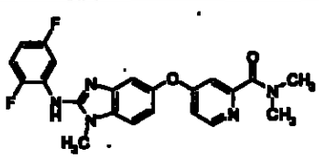
The solution of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carboxylic acid dimethylamide in methanol was treated with 10% palladium on carbon and stirred under hydrogen atmosphere for 3 hours at room temperature. The mixture was purged with nitrogen and then was filtered through celite and the filtrate was concentrated to provide the diamine. HPLC, 1.17 min; MS: MH+ = 287.1

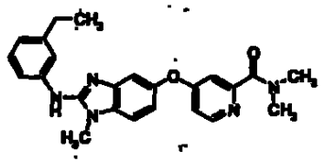
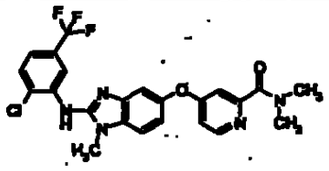
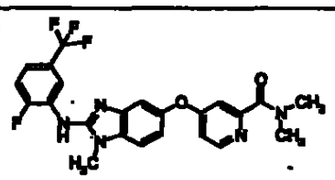
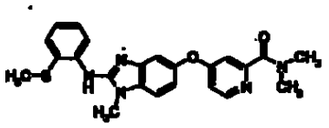
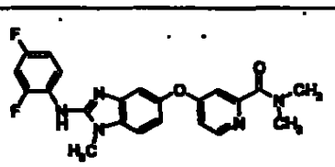
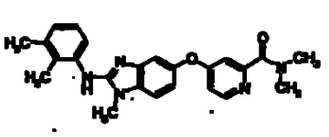
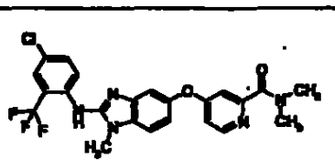
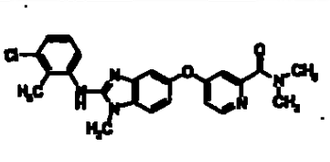
Step 5. Synthesis of 4-[2-(2,6-Difluoro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid dimethylamide:

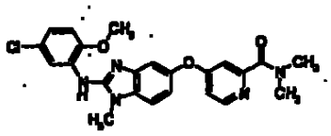
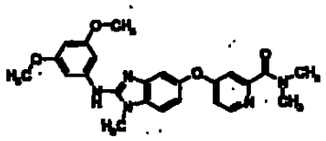
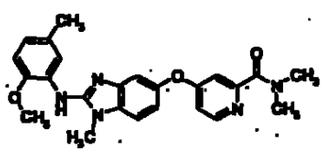
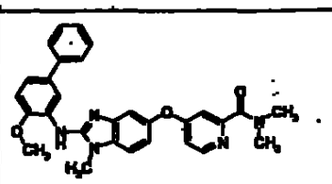
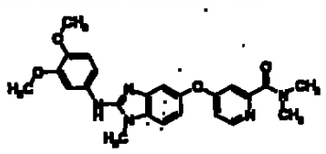
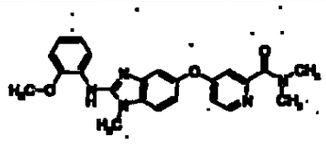
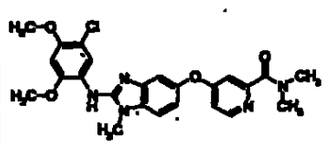
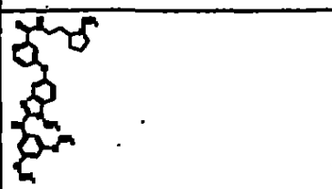
A solution of the 4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carboxylic acid dimethylamide (1eq) in methanol was treated with 2,6-difluorophenylisothiocyanate (1eq) and stirred overnight. To the reaction mixture, methyl iodide (1eq) was added and stirred overnight at 60°C. The reaction was cooled down to room temperature, evaporated, and the residue purified by reverse phase HPLC. HPLC, 1.66 min; MS: MH+ = 424.1

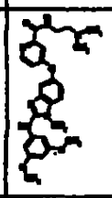
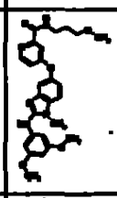
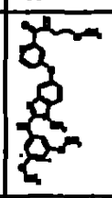
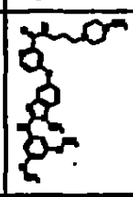
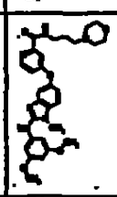
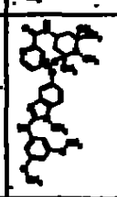
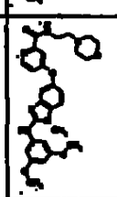
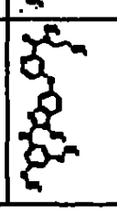
Each of the compounds 823-984, listed in the below table were synthesized as indicated in the right hand column by the method described herein.

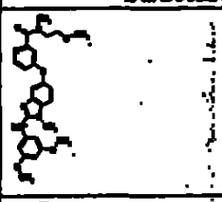
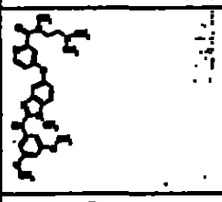
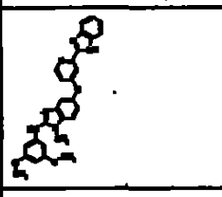
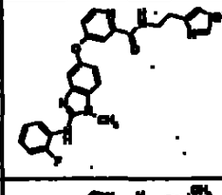
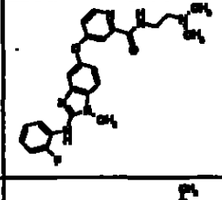
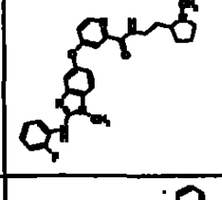
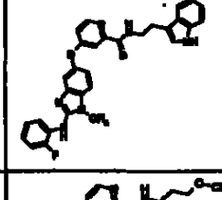
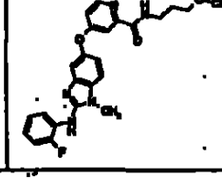
Table 13

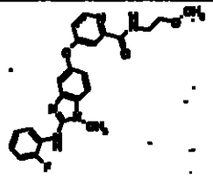
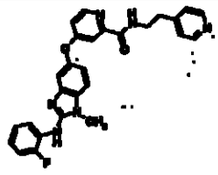
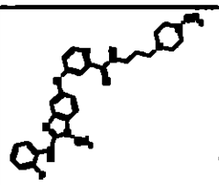
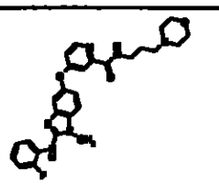
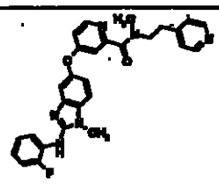
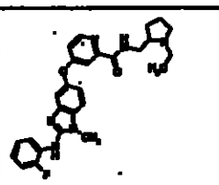
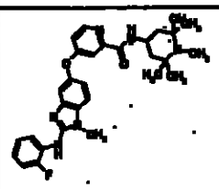
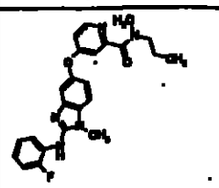
Example	Structure	Name	MH+	Synthesized as in Ex.:
823		4-({2-[(2,6-difluorophenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide	424.1	822
824		N,N-dimethyl-4-[(1-methyl-2-{[2-(trifluoromethyl)phenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	456.4	822
825		4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N,N-dimethylpyridine-2-carboxamide	416.5	822
826		4-({2-[(3,5-difluorophenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide	424.4	822
827		4-({2-[(2,4-dimethylphenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide	416.5	822
828		N,N-dimethyl-4-{[1-methyl-2-({2-[(trifluoromethyl)oxy]-phenyl}amino)-1H-benz-imidazol-5-yl]oxy}pyridine-2-carboxamide	472.4	822
829		4-({2-[(2,5-difluorophenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide	424.4	822

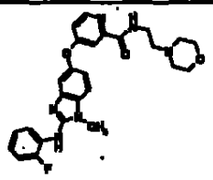
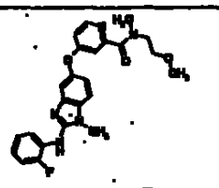
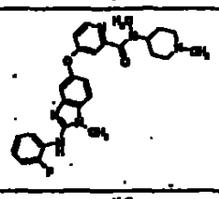
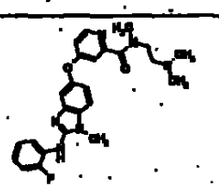
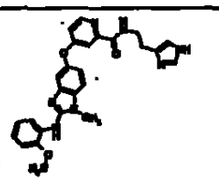
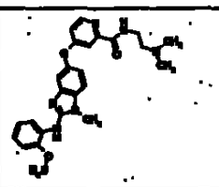
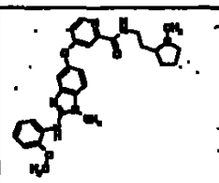
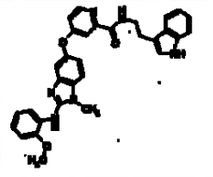
Example	Structure	Name	MH+	Synthesized as in Ex.:
830		4-({2-[(3-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N,N-dimethylpyridine-2-carboxamide	416.5	822
831		4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N,N-dimethylpyridine-2-carboxamide	490.9	822
832		4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N,N-dimethylpyridine-2-carboxamide	474.4	822
833		N,N-dimethyl-4-[(1-methyl-2-{[2-(methylthio)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	434.5	822
834		4-({2-[(2,4-difluorophenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide	424.4	822
835		4-({2-[(2,3-dimethylphenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide	416.5	822
836		4-[(2-{[4-chloro-2-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N,N-dimethylpyridine-2-carboxamide	490.9	822
837		4-({2-[(3-chloro-2-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide	436.9	822

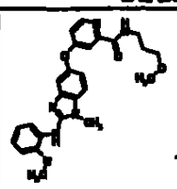
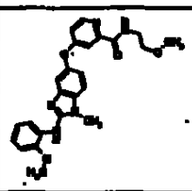
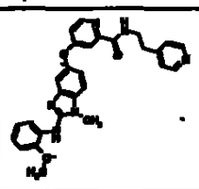
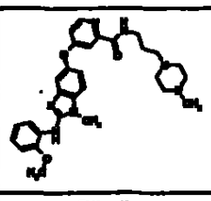
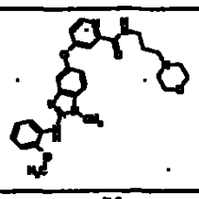
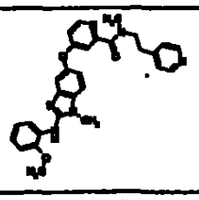
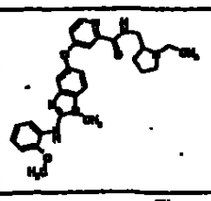
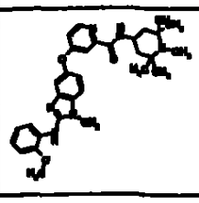
Example	Structure	Name	MH+	Synthesized as in Ex.:
838		4-[(2-{[5-chloro-2-(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N,N-dimethylpyridine-2-carboxamide	452.9	822
839		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N,N-dimethylpyridine-2-carboxamide	448.5	822
840		N,N-dimethyl-4-[(1-methyl-2-{[5-methyl-2-(methyloxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	432.5	822
841		N,N-dimethyl-4-[(1-methyl-2-{[4-(methyloxy)-1,1'-biphenyl-3-yl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	494.6	822
842		4-[(2-{[3,4-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N,N-dimethylpyridine-2-carboxamide	448.5	822
843		N,N-dimethyl-4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	418.5	822
844		4-[(2-{[5-chloro-2,4-bis(methyloxy)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N,N-dimethylpyridine-2-carboxamide	482.9	822
845		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-pyridine-2-carboxamide	531.6	372

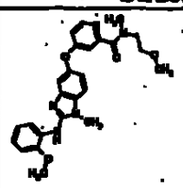
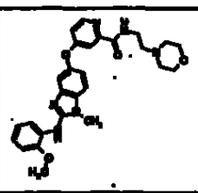
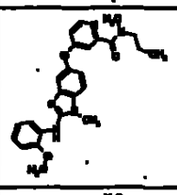
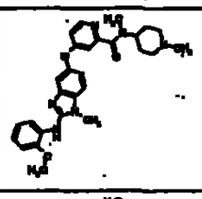
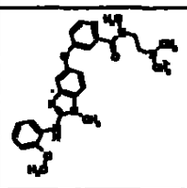
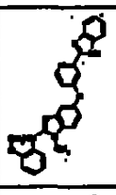
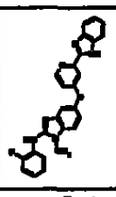
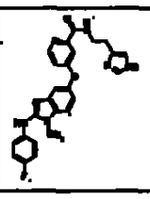
Example	Structure	Name	MH+	Synthesized as in Ex.:
846		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(dimethylamino)ethyl]pyridine-2-carboxamide	491.6	372
847		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(methyloxy)propyl]pyridine-2-carboxamide	492.5	372
848		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(methyloxy)ethyl]pyridine-2-carboxamide	478.5	372
849		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[3-(4-methylpiperazin-1-yl)propyl]-pyridine-2-carboxamide	560.7	372
850		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(3-morpholin-4-ylpropyl)pyridine-2-carboxamide	547.6	372
851		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)pyridine-2-carboxamide	573.7	372
852		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	533.6	372
853		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methyl-N-propylpyridine-2-carboxamide	476.5	372

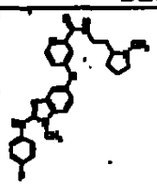
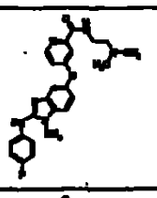
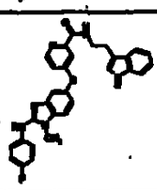
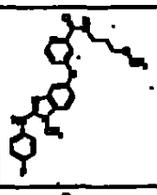
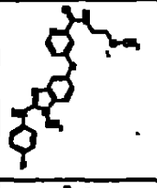
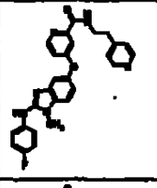
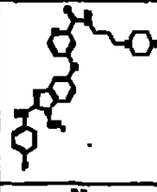
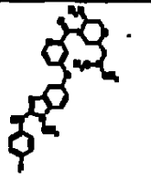
Example	Structure	Name	MH+	Synthesized as in Ex.:
854		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methyl-N-[2-(methyloxy)-ethyl]pyridine-2-carboxamide	492.5	372
855		4-[(2-{[3,5-bis(methyloxy)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-[2-(dimethylamino)ethyl]-N-methylpyridine-2-carboxamide	505.6	372
856		5-{[2-(1H-benzimidazol-2-yl)-pyridin-4-yl]oxy}-N-[3,5-bis-(methyloxy)phenyl]-1-methyl-1H-benzimidazol-2-amine	493.5	821
857		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1H-imidazol-4-yl)ethyl]pyridine-2-carboxamide	472.5	372
858		N-[2-(dimethylamino)ethyl]-4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridine-2-carboxamide	449.5	372
859		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	489.6	372
860		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1H-indol-3-yl)-ethyl]pyridine-2-carboxamide	521.6	372
861		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(methyloxy)-propyl]pyridine-2-carboxamide	450.5	372

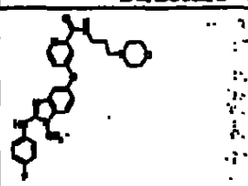
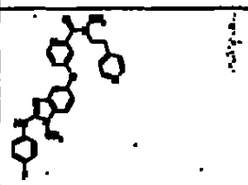
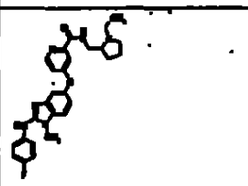
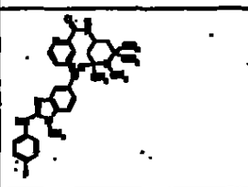
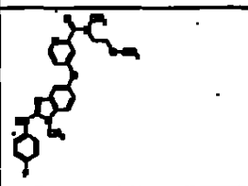
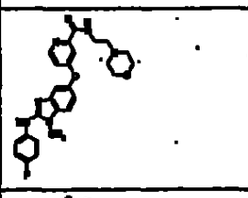
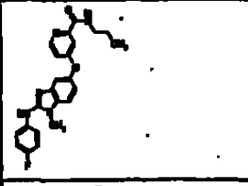
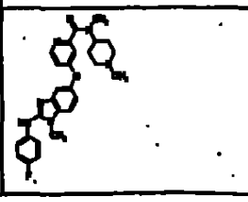
Example	Structure	Name	MH+	Synthesized as in Ex.:
862		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(methyloxy)-ethyl]pyridine-2-carboxamide	436.5	372
863		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	483.5	372
864		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(4-methyl-piperazin-1-yl)propyl]pyridine-2-carboxamide	518.6	372
865		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(3-morpholin-4-yl-propyl)pyridine-2-carboxamide	505.6	372
866		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-(2-pyridin-4-ylethyl)pyridine-2-carbox-amide	497.5	372
867		N-[(1-ethylpyrrolidin-2-yl)-methyl]-4-({2-[(2-fluorophenyl)-amino]-1-methyl-1H-benz-imidazol-5-yl}oxy)pyridine-2-carboxamide	489.6	372
868		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(1,2,2,6,6-penta-methylpiperidin-4-yl)pyridine-2-carboxamide	531.6	372
869		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-propyl-pyridine-2-carboxamide	434.5	372

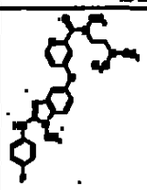
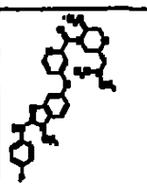
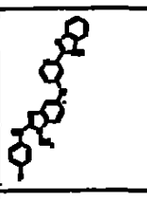
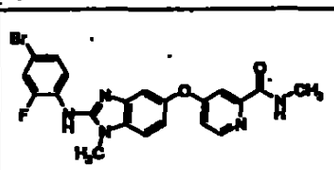
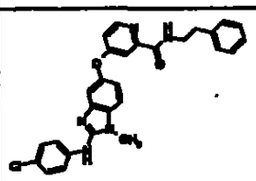
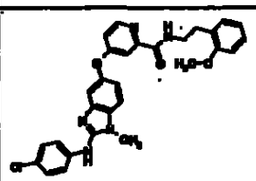
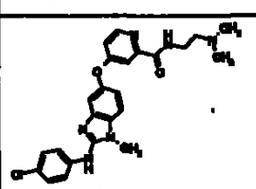
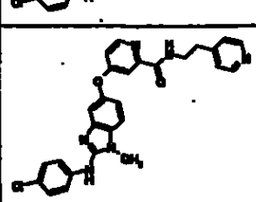
Example	Structure	Name	MH+	Synthesized as in Ex.:
870		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-morpholin-4-yl-ethyl)pyridine-2-carboxamide	491.5	372
871		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-[2-(methyl-oxy)ethyl]pyridine-2-carbox-amide	450.5	372
872		4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-(1-methyl-piperidin-4-yl)pyridine-2-carboxamide	489.6	372
873		N-[2-(dimethylamino)ethyl]-4-{{2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	463.5	372
874		N-[2-(1H-imidazol-4-yl)ethyl]-4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	484.5	372
875		N-[2-(dimethylamino)ethyl]-4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	461.5	372
876		4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-pyridine-2-carboxamide	501.6	372
877		N-[2-(1H-indol-3-yl)ethyl]-4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	533.6	372

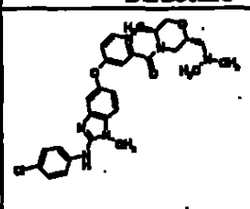
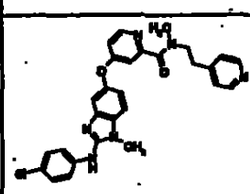
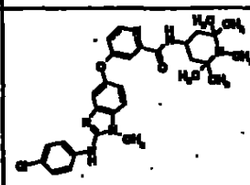
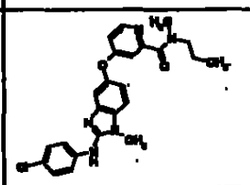
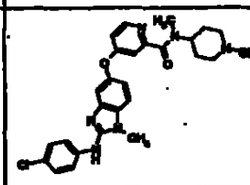
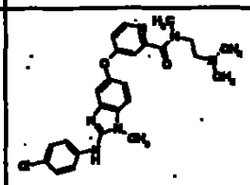
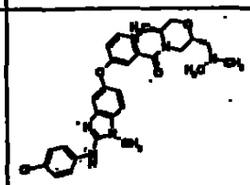
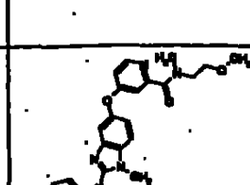
Example	Structure	Name	MH+	Synthesized as in Ex.:
878		4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]-N-[3-(methyloxy)propyl]pyridine-2-carboxamide	462.5	372
879		4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]-N-[2-(methyloxy)ethyl]pyridine-2-carboxamide	448.5	372
880		4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]-N-(2-pyridin-4-ylethyl)pyridine-2-carboxamide	495.6	372
881		4-[(1-methyl-2-{[2-(methyl-oxy)phenyl]amino}-1H-benz-imidazol-5-yl)oxy]-N-[3-(4-methylpiperazin-1-yl)propyl]-pyridine-2-carboxamide	530.6	372
882		4-[(1-methyl-2-{[2-(methyloxy)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]-N-(3-morpholin-4-ylpropyl)pyridine-2-carboxamide	517.6	372
883		N-methyl-4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-pyridin-4-ylethyl)pyridine-2-carboxamide	509.6	372
884		N-[(1-ethylpyrrolidin-2-yl)-methyl]-4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	501.6	372
885		4-[(1-methyl-2-{[2-(methyl-oxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)pyridine-2-carboxamide	543.7	372

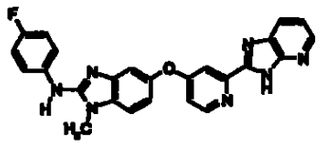
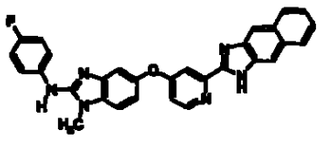
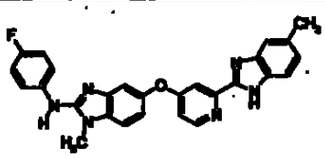
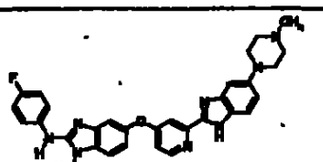
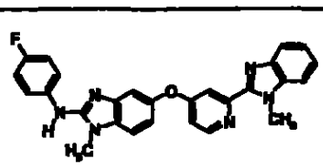
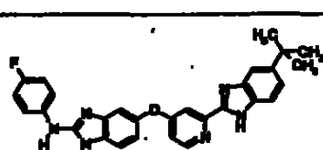
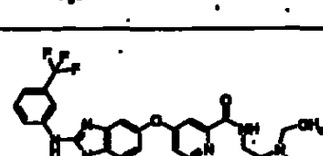
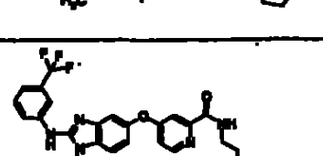
Example	Structure	Name	MH+	Synthesized as in Ex.:
886		N-methyl-4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-[2-(methyloxy)ethyl]pyridine-2-carboxamide	462.5	372
887		4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	503.6	372
888		N-methyl-4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-propylpyridine-2-carboxamide	446.5	372
889		N-methyl-4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(1-methylpiperidin-4-yl)pyridine-2-carboxamide	501.6	372
890		N-[2-(dimethylamino)ethyl]-N-methyl-4-[(1-methyl-2-{[2-(methyloxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	475.6	372
891		5-{[2-(1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[2-(methyloxy)phenyl]-1H-benzimidazol-2-amine	463.5	372
892		5-{[2-(1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-N-(2-fluorophenyl)-1-methyl-1H-benzimidazol-2-amine	451.5	372
893		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1H-imidazol-4-yl)ethyl]pyridine-2-carboxamide	472.5	372

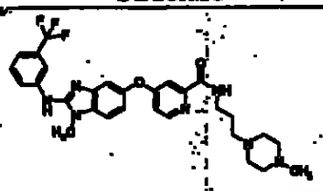
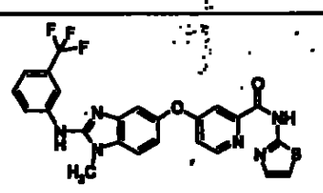
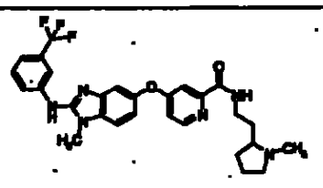
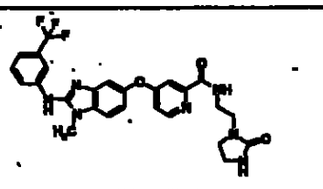
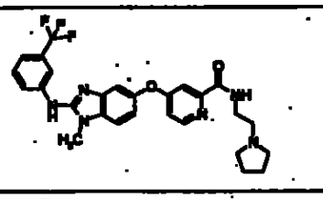
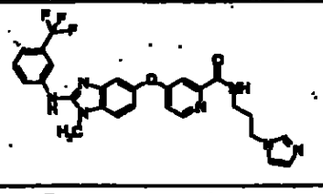
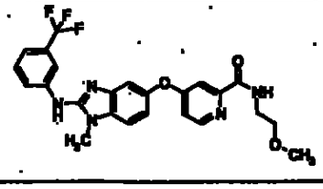
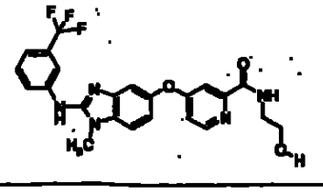
Example	Structure	Name	MH+	Synthesized as in Ex.:
894		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1-methyl-pyrrolidin-2-yl)ethyl]pyridine-2-carboxamide	489.6	372
895		N-[2-(dimethylamino)ethyl]-4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	449.6	372
896		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(1H-indol-3-yl)-ethyl]pyridine-2-carboxamide	521.6	372
897		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(methyloxy)-propyl]pyridine-2-carboxamide	450.5	372
898		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(methyloxy)-ethyl]pyridine-2-carboxamide	436.5	372
899		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	483.6	372
900		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[3-(4-methyl-piperazin-1-yl)propyl]pyridine-2-carboxamide	518.6	372
901		5-{[2-({(2R,5R)-2-[(dimethyl-amino)methyl]-5-methyl-morpholin-4-yl}carbonyl)-pyridin-4-yl]oxy}-N-(4-fluoro-phenyl)-1-methyl-1H-benz-imidazol-2-amine	519.6	372

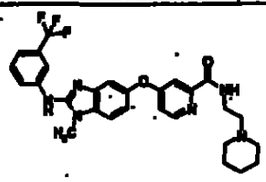
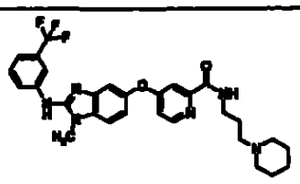
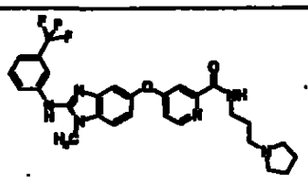
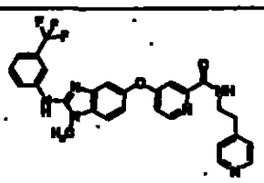
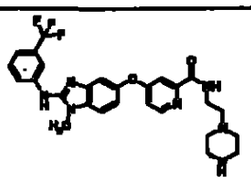
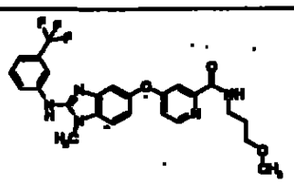
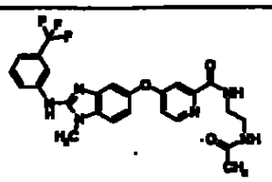
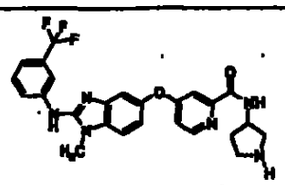
Example	Structure	Name	MH+	Synthesized as in Ex.:
902		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(3-morpholin-4-yl-propyl)pyridine-2-carboxamide	505.6	372
903		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-(2-pyridin-4-ylethyl)pyridine-2-carbox-amide	497.6	372
904		N-[(1-ethylpyrrolidin-2-yl)-methyl]-4-({2-[(4-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	489.6	372
905		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(1,2,2,6,6-penta-methylpiperidin-4-yl)pyridine-2-carboxamide	531.7	372
906		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-[2-(methyl-oxy)ethyl]pyridine-2-carbox-amide	450.6	372
907		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-morpholin-4-yl-ethyl)pyridine-2-carboxamide	491.6	372
908		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-propylpyridine-2-carboxamide	434.6	372
909		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-(1-methyl-piperidin-4-yl)pyridine-2-carboxamide	489.6	372

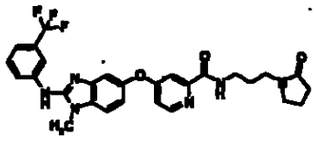
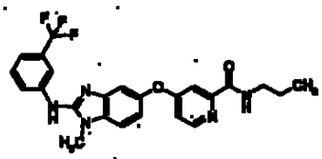
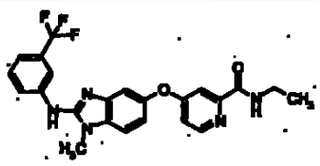
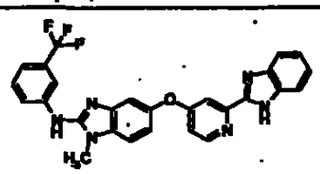
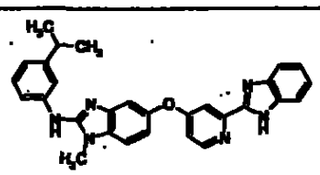
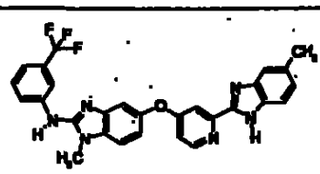
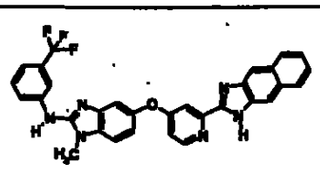
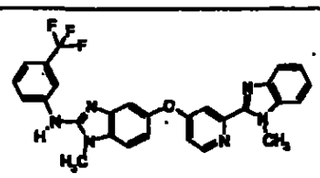
Example	Structure	Name	MH+	Synthesized as in Ex.:
910		N-[2-(dimethylamino)ethyl]-4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)-N-methylpyridine-2-carboxamide	463.6	372
911		5-{[2-({(2R,5S)-2-[(dimethyl-amino)methyl]-5-methyl-morpholin-4-yl}carbonyl)-pyridin-4-yl]oxy}-N-(4-fluoro-phenyl)-1-methyl-1H-benz-imidazol-2-amine	519.6	372
912		5-{[2-(1H-benzimidazol-2-yl)-pyridin-4-yl]oxy}-N-(4-fluoro-phenyl)-1-methyl-1H-benz-imidazol-2-amine	451.5	821
913		4-({2-[(4-bromo-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	471.3	120a
914		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-phenylethyl)-pyridine-2-carboxamide	499.0	372
915		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-{2-[2-(methyloxy)-phenyl]ethyl}pyridine-2-carbox-amide	529.0	372
916		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(dimethylamino)-ethyl]pyridine-2-carboxamide	466.0	372
917		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-pyridin-4-ylethyl)-pyridine-2-carboxamide	500.0	372

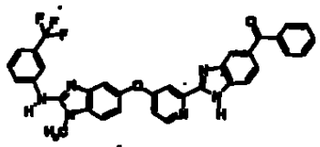
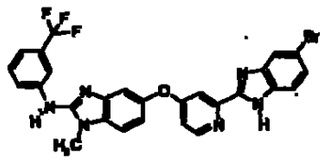
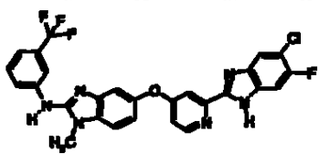
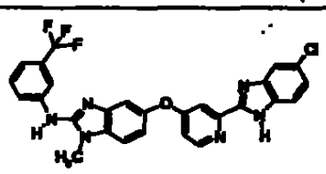
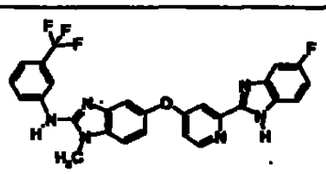
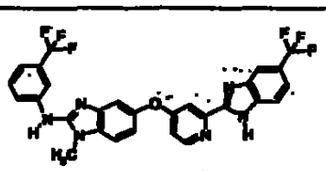
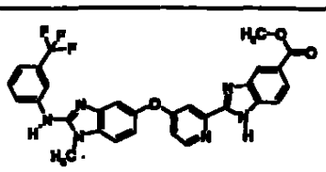
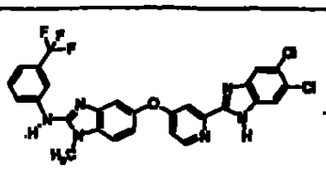
Example	Structure	Name	MH+	Synthesized as in Ex.:
918		N-(4-chlorophenyl)-5-{[2-({(2R,5R)-2-[(dimethylamino)-methyl]-5-methylmorpholin-4-yl}carbonyl)pyridin-4-yl]oxy}-1-methyl-1H-benzimidazol-2-amine	536.0	372
919		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-(2-pyridin-4-ylethyl)pyridine-2-carboxamide	514.0	372
920		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(1,2,2,6,6-penta-methylpiperidin-4-yl)pyridine-2-carboxamide	548.1	372
921		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-propyl-pyridine-2-carboxamide	450.9	372
922		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-(1-methyl-piperidin-4-yl)pyridine-2-carboxamide	506.0	372
923		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(dimethylamino)-ethyl]-N-methylpyridine-2-carboxamide	480.0	372
924		N-(4-chlorophenyl)-5-{[2-({(2R,5S)-2-[(dimethylamino)-methyl]-5-methylmorpholin-4-yl}carbonyl)pyridin-4-yl]oxy}-1-methyl-1H-benzimidazol-2-amine	536.0	372
925		4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methyl-N-[2-(methyl-oxy)ethyl]pyridine-2-carbox-amide	466.9	372

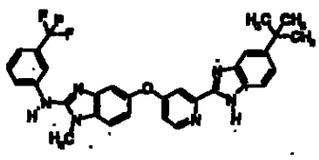
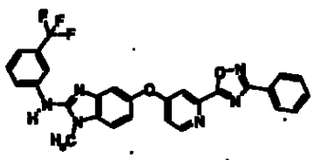
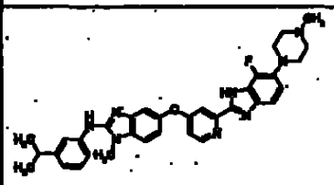
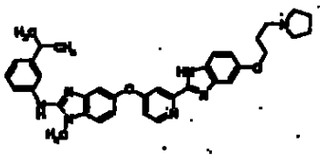
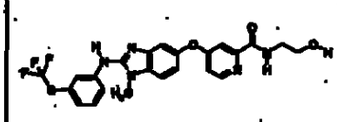
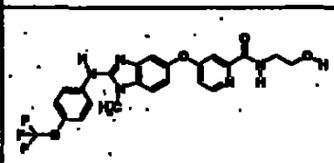
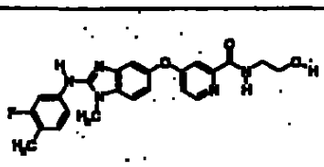
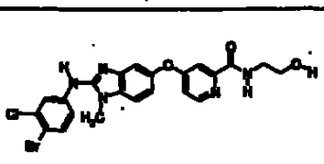
Example	Structure	Name	MH+	Synthesized as in Ex.:
926		N-(4-fluorophenyl)-5-{[2-(3H-imidazo[4,5-b]pyridin-2-yl)-pyridin-4-yl]oxy}-1-methyl-1H-benzimidazol-2-amine	452.5	821
927		N-(4-fluorophenyl)-1-methyl-5-{[2-(1H-naphtho[2,3-d]-imidazol-2-yl)pyridin-4-yl]oxy}-1H-benzimidazol-2-amine	501.5	821
928		N-(4-fluorophenyl)-1-methyl-5-{[2-(5-methyl-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1H-benzimidazol-2-amine	465.5	821
929		N-(4-fluorophenyl)-1-methyl-5-({2-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]pyridin-4-yl}oxy)-1H-benzimidazol-2-amine	549.6	821
930		N-(4-fluorophenyl)-1-methyl-5-{[2-(1-methyl-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1H-benzimidazol-2-amine	465.5	821
931		5-({2-[5-(1,1-dimethylethyl)-1H-benzimidazol-2-yl]pyridin-4-yl}oxy)-N-(4-fluorophenyl)-1-methyl-1H-benzimidazol-2-amine	507.6	821
932		N-[(1-ethylpyrrolidin-2-yl)-methyl]-4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	539.3	372
933		4-[(1-methyl-2-{[3-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide	541.3	372

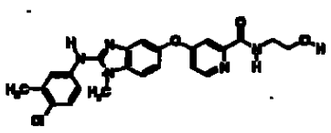
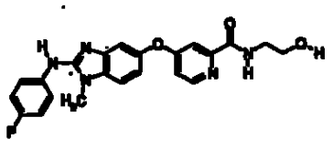
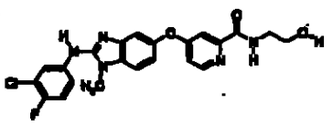
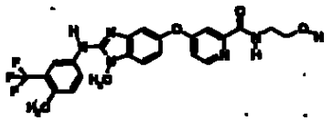
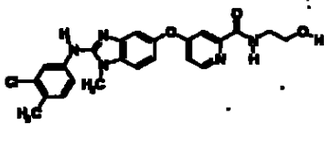
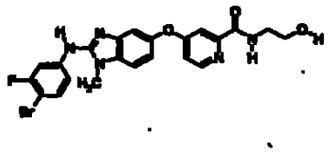
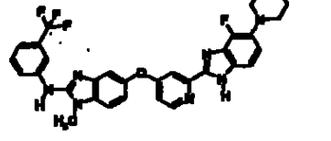
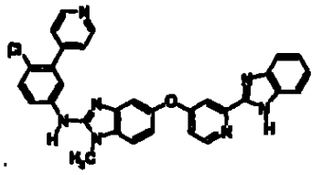
Example	Structure	Name	MH+	Synthesized as in Ex.:
934		N-[3-(4-methylpiperazin-1-yl)-propyl]-4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	568.4	372
935		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-1,3-thiazol-2-ylpyridine-2-carboxamide	511.2	372
936		N-[2-(1-methylpyrrolidin-2-yl)-ethyl]-4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	539.3	372
937		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-[2-(2-oxoimidazolidin-1-yl)ethyl]-pyridine-2-carboxamide	540.3	372
938		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-pyrrolidin-1-ylethyl)pyridine-2-carboxamide	525.3	372
939		N-[3-(1H-imidazol-1-yl)propyl]-4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	536.3	372
940		N-[2-(methyloxy)ethyl]-4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	486.3	372
941		N-(2-hydroxyethyl)-4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	472.2	372

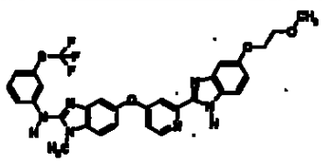
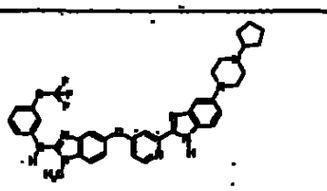
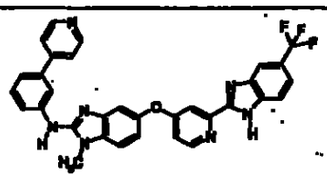
Example	Structure	Name	MH+	Synthesized as in Ex.:
942		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-piperidin-1-ylethyl)pyridine-2-carboxamide	539.3	372
943		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(3-piperidin-1-ylpropyl)pyridine-2-carboxamide	553.3	372
944		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(3-pyrrolidin-1-ylpropyl)pyridine-2-carboxamide	539.3	372
945		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-pyridin-4-ylethyl)pyridine-2-carboxamide	533.3	372
946		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-(2-piperazin-1-ylethyl)pyridine-2-carboxamide	540.2	372
947		N-[3-(methyloxy)propyl]-4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	500.2	372
948		N-[2-(acetylamino)ethyl]-4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	513.3	372
949		4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-pyrrolidin-3-ylpyridine-2-carboxamide	497.2	372

Example	Structure	Name	MH+	Synthesized as in Ex.:
950		4-[(1-methyl-2-{[3-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-[3-(2-oxopyrrolidin-1-yl)propyl]-pyridine-2-carboxamide	553.3	372
951		4-[(1-methyl-2-{[3-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-propylpyridine-2-carboxamide	470.3	372
952		N-ethyl-4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	456.2	372
953		5-{[2-(1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	501.2	821
954		5-{[2-(1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[3-(1-methylethyl)phenyl]-1H-benzimidazol-2-amine	abran	821
955		1-methyl-5-{[2-(5-methyl-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-N-[3-(trifluoromethyl)-phenyl]-1H-benzimidazol-2-amine	515.2	821
956		1-methyl-5-{[2-(1H-naphtho[2,3-d]imidazol-2-yl)-pyridin-4-yl]oxy}-N-[3-(tri-fluoromethyl)phenyl]-1H-benzimidazol-2-amine	551.3	821
957		1-methyl-5-{[2-(1-methyl-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-N-[3-(trifluoromethyl)-phenyl]-1H-benzimidazol-2-amine	515.2	821

Example	Structure	Name	MH+	Synthesized as in Ex.:
958		(2-{4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-1H-benzimidazol-5-yl)(phenyl)methanone	605.2	821
959		5-{[2-(5-bromo-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	579.1	821
960		5-{[2-(5-chloro-6-fluoro-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	553.2	821
961		5-{[2-(5-chloro-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	535.2	821
962		5-{[2-(5-fluoro-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	519.4	821
963		1-methyl-5-({2-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]pyridin-4-yl}oxy)-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	569.2	821
964		methyl 2-{4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1H-benzimidazole-5-carboxylate	559.2	821
965		5-{[2-(5,6-dichloro-1H-benzimidazol-2-yl)pyridin-4-yl]oxy}-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	569.1	821

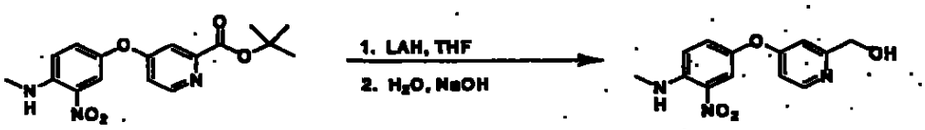
Example	Structure	Name	MH+	Synthesized as in Ex.:
966		5-({2-[5-(1,1-dimethylethyl)-1H-benzimidazol-2-yl]pyridin-4-yl}oxy)-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	557.3	821
967		1-methyl-5-{[2-(3-phenyl-1,2,4-oxadiazol-5-yl)pyridin-4-yl]oxy}-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	529.2	821
968		5-({2-[7-fluoro-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]pyridin-4-yl}oxy)-1-methyl-N-[3-(1-methylethyl)phenyl]-1H-benzimidazol-2-amine	591.3	821
969		1-methyl-N-[3-(1-methyl-ethyl)phenyl]-5-[(2-{5-[(3-pyrrolidin-1-ylpropyl)oxy]-1H-benzimidazol-2-yl}pyridin-4-yl)oxy]-1H-benzimidazol-2-amine	602.7	821
970		N-(2-hydroxyethyl)-4-{[1-methyl-2-({3-[(trifluoromethyl)-thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	504.1	820
971		N-(2-hydroxyethyl)-4-{[1-methyl-2-({4-[(trifluoromethyl)-thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}-pyridine-2-carboxamide	504.1	820
972		4-({2-[(3-fluoro-4-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	436.2	820
973		4-({2-[(4-bromo-3-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	516	820

Example	Structure	Name	MH+	Synthesized as in Ex.:
974		4-({2-[(4-chloro-3-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	452.2	820
975		4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)-pyridine-2-carboxamide	422.2	820
976		4-({2-[(3-chloro-4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	456.2	820
977		N-(2-hydroxyethyl)-4-[(1-methyl-2-{[4-methyl-3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	486.2	820
978		4-({2-[(3-chloro-4-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	452.2	820
979		4-({2-[(4-bromo-3-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide	502.1	820
980		5-({2-[4-fluoro-5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]pyridin-4-yl}oxy)-1-methyl-N-[3-(trifluoromethyl)phenyl]-1H-benzimidazol-2-amine	428.2	821
981		5-{[2-(1H-benzimidazol-2-yl)-pyridin-4-yl]oxy}-N-(4-chloro-3-pyridin-4-ylphenyl)-1-methyl-1H-benzimidazol-2-amine	545.0	821

Example	Structure	Name	MH+	Synthesized as in Ex.:
982		1-methyl-5-{[2-(5-{[2-(methyl-oxy)ethyl]oxy}-1H-benz-imidazol-2-yl)pyridin-4-yl]oxy}-N-{3-[(trifluoromethyl)thio]-phenyl}-1H-benzimidazol-2-amine	607.2	821
983		5-({2-[5-(4-cyclopentyl-piperazin-1-yl)-1H-benz-imidazol-2-yl]pyridin-4-yl}oxy)-1-methyl-N-{3-[(trifluoro-methyl)thio]phenyl}-1H-benzimidazol-2-amine	685.3	821
984		1-methyl-N-(3-pyridin-4-yl-phenyl)-5-({2-[5-(trifluoro-methyl)-1H-benzimidazol-2-yl]pyridin-4-yl}oxy)-1H-benzimidazol-2-amine	578.3	821

Example 985: Synthesis of Oxime Series: 4-[2-(4-Bromo-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carbaldehyde oxime

Step 1. Synthesis of [4-(4-Methylamino-3-nitro-phenoxy)-pyridin-2-yl]-methanol

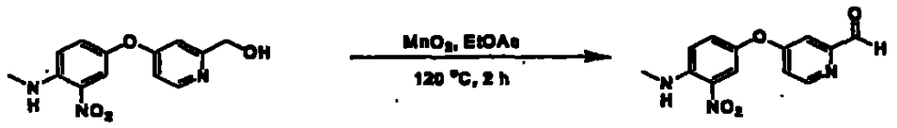


1 2

A flame dried 500 mL three-necked round bottom flask purged with N_2 was charged with LAH (2.32 g, 58.0 mmol) and dry THF (60 mL). The resulting suspension was cooled to 0 °C and a suspension of *t*-butyl ester 1 (10.0 g, 29.0 mmol) in dry THF (60 mL) was slowly added while keeping the internal reaction temperature under 5 °C. The reaction was stirred at 0 °C for 30 min then at rt for 30 min. After the reaction was judged complete, the mixture was treated with successive dropwise addition of water (2.3 mL), 10 % NaOH (2.3 mL), and water (7.2 mL). The resulting suspension was filtered through Celite, washed with ethyl acetate and methanol, and the collected organics

concentrated. The crude product was absorbed onto silica gel and purified by flash chromatography (97: 3 CH_2Cl_2/MeOH) to give 2 as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 5.5 Hz, 1 H), 8.05 (br s, 1H), 7.96 (d, J = 2.75 Hz, 1 H), 7.29 (d, J = 2.75 Hz, 1 H), 6.92 (d, J = 9.35 Hz, 1 H), 6.75 (m, 2 H), 4.68 (s, 2 H), 3.07 (d, J = 5.23 Hz, 3 H).

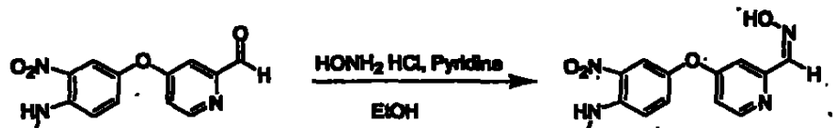
Step 2. Synthesis of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carbaldehyde



1 2

A 250 mL reaction tube was charged with benzyl alcohol 1 (1.0 g, 3.6 mmol), MnO_2 (4.7 g, 54 mmol) and EtOAc (20 mL). The reaction tube was sealed was heated to 120 °C with stirring for 2 h. The reaction was allowed to cool to rt, then filtered through Celite and washed successively with EtOAc, MeOH, and EtOH. The combine organics were concentrated to give 936 mg (3.4 mmol, 94%) of 2 as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1 H), 8.64 (d, J = 5.5 Hz, 1 H), 8.09 (br s, 1 H), 7.96 (d, J = 2.75 Hz, 1 H), 7.37 (d, J = 2.48 Hz, 1 H), 7.29 (d, J = 2.75 Hz, 1 H), 7.08 (dd, J = 2.47, 5.5 Hz, 1 H), 6.94 (d, J = 9.35 Hz, 1 H), 3.08 (d, J = 5.23 Hz, 3 H).

Step 3. Synthesis of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carbaldehyde oxime

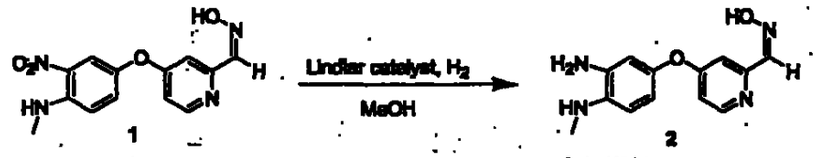


1 2

A 50 mL round bottom flask was charged with 1 (680 mg, 2.5 mmol), hydroxylamine HCl (191 mg, 2.75 mmol), pyridine (0.25 mL, 3.0 mmol) and ethanol (10 mL). The resulting reaction mixture was stirred at rt overnight. The crude product was concentrated, absorbed onto silica gel, and purified by flash chromatography (97: 3 CH_2Cl_2/MeOH to give 2 as an orange solid. LCMS m/z 289.2 (MH^+), t_R = 2.06 min.

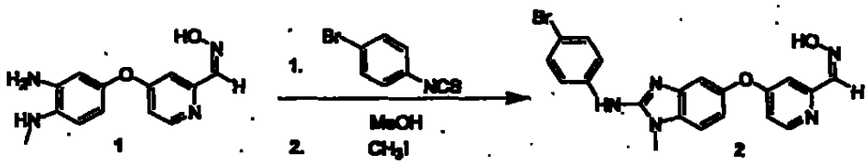
114

Step 4. Synthesis of 4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carbaldehyde oxime



A reaction tube was charged with suspension of 1 (330 mg, 1.15 mmol) and Lindlar catalyst (245 mg, 10 mol %) in methanol (5 mL), sealed, and placed on a Parr shaker. The reaction was pressurized with H_2 (60 psi) and maintained for 1 h. The reaction was filtered through Celite and the remaining solids were washed with MeOH. The combined organics were concentrated to give 2 as a brown semi-solid which was taken on without further purification.

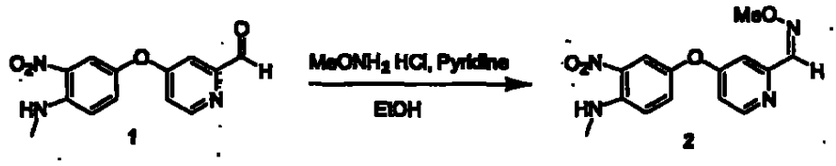
Step 5. Synthesis of 4-[2-(4-Bromo-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carbaldehyde oxime



A 5 mL round bottom flask was charged with 4-bromophenylisothiocyanate (54 mg, 0.25 mmol), diamine 1 (65 mg, 0.25 mmol), and MeOH (1 mL). The resulting reaction was maintained at rt overnight. Methyl iodide (20 µL, 0.33 mmol) was added to the reaction and stirred overnight. The reaction was concentrated and the resulting residue was purified by reverse-phase HPLC. LCMS *m/z* 438.1 (MH^+), t_R = 1.87 min.

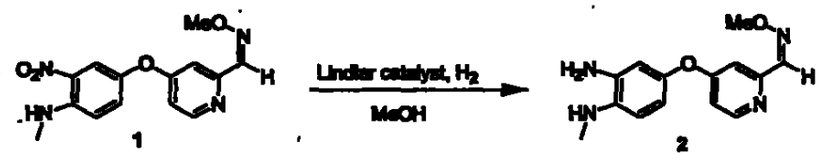
Example 986: Synthesis of *O*-methyl-oxime Series: 4-[1-Methyl-2-(4-trifluoromethylsulfanyl-phenylamino)-1H-benzoimidazol-5-yloxy]-pyridine-2-carbaldehyde *O*-methyl-oxime

Step 1. Synthesis of 4-(4-Methylamino-3-nitro-phenoxy)-pyridine-2-carbaldehyde *O*-methyl-oxime



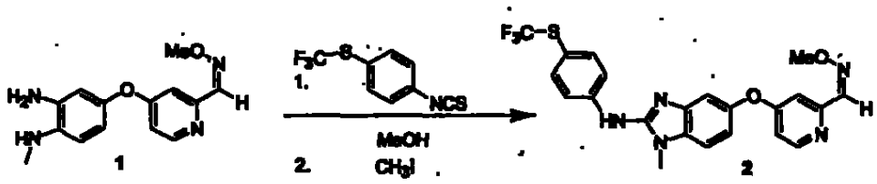
A 25 mL round bottom flask was charged with a suspension of 1 (600 mg, 2.2 mmol), methoxylamine HCl (202 mg, 2.42 mmol), and pyridine (0.22 mL, 2.6 mmol) in ethanol (9 mL). The resulting reaction mixture was stirred at rt overnight. The crude product was concentrated, absorbed onto silica gel, and purified by flash chromatography (97: 3 CH_2Cl_2/MeOH) to give 2 as an orange solid. LCMS *m/z* 303.2 (MH^+), t_R = 2.40 min.

Step 2. Synthesis of 4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carbaldehyde *O*-methyl-oxime



A reaction tube was charged with a suspension of 1 (270 mg, 0.9 mmol) and Lindlar catalyst (192 mg, 10 mol %) in methanol (5 mL), and was then placed on a Parr shaker. The was reaction pressurized with H_2 (60 psi) and maintained for 1 h. The reaction was filtered through Celite and the remained solids were washed with methanol. The combined organics were concentrated to give 2 as a brown semi-solid which was carried forward without further purification LCMS *m/z* 273.3 (MH^+), t_R = 1.56 min.

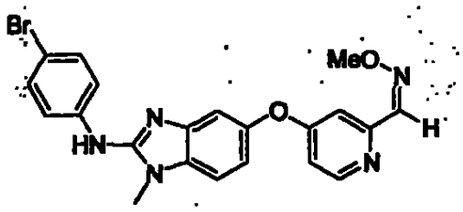
Step 3. Synthesis of 4-[1-Methyl-2-(4-trifluoromethylsulfanyl-phenylamino)-1H-benzoimidazol-5-yloxy]-pyridine-2-carbaldehyde *O*-methyl-oxime



A 5 mL round bottom flask was charged with 4-trifluoromethylthio-phenylisothiocyanate (24 mg, 0.1 mmol), diamine 1 (27 mg, 0.1 mmol), and MeOH (0.5 mL). The reaction was maintained at rt overnight, after which methyl iodide (8 µL, 0.13

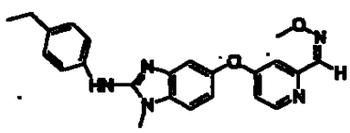
mmol) was added. After 16 h, the reaction was concentrated and the resulting residue was purified by reverse-phase HPLC. LCMS *m/z* 474.3 (MH^+), t_R = 2.42 min.

Example 987



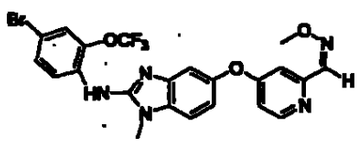
Synthesized as described in Example 986 step 3 using 4-bromophenyl isothiocyanate. LCMS *m/z* 402.4 (MH^+), t_R = 2.15 min.

Example 988



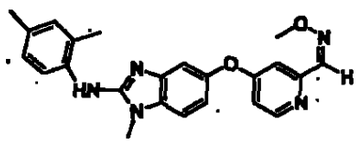
Synthesized as described in Example 986 step 3 using 4-ethylphenylisiothiocyanate. LCMS *m/z* 402.4 (MH^+), t_R = 2.15 min.

Example 989



Synthesized as described in Example 986 step 3 using 4-bromo-2-trifluoro-methoxyphenylisothiocyanate. LCMS *m/z* 536.2 (MH^+), t_R = 2.38 min.

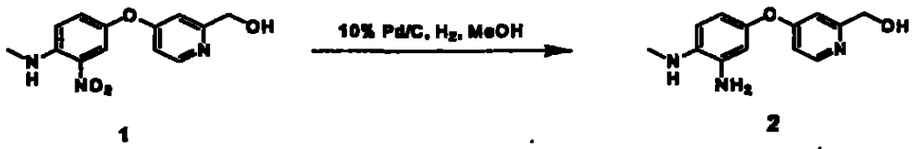
Example 990



Synthesized as described in Example 986 step 3 using 2,4-dimethylphenylisothiocyanate. LCMS *m/z* 402, (MH^+), t_R = 2.07 min.

Example 991: Synthesis of Benzyl Alcohol Series: {4-[2-(4-Chloro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridin-2-yl}-methanol

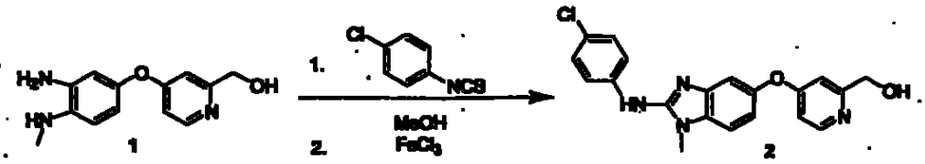
Step 1. Synthesis of [4-(3-Amino-4-methylamino-phenoxy)-pyridin-2-yl]-methanol



1 2

A suspension of nitroaniline 1 (550 mg, 2.0 mmol) in methanol was sparged with N_2 for 20 min after which 10% Pd/C (106 mg, 0.1 mmol) was added. The reaction was charged with H_2 and maintained under a H_2 atmosphere overnight at rt. The reaction was sparged with N_2 and filtered through Celite. The collected solids were washed with EtOAc (3 X 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to afford 2, which was taken on without further purification.

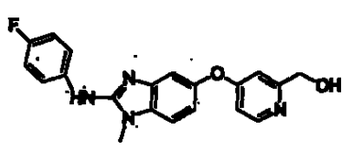
Step 2. Synthesis of {4-[2-(4-Chloro-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridin-2-yl}-methanol.



1 2

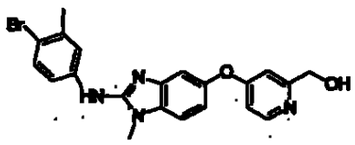
A 5 mL round bottom flask was charged with 4-chlorophenylisothiocyanate (34 g, 0.2 mmol), diamine 1 (49 mg, 0.2 mmol), and MeOH (1 mL) and the resulting reaction was maintained at rt overnight. Ferric chloride (16 mg, 0.1 mmol) was added and the red reaction mixture was stirred overnight. The reaction was partitioned with EtOAc and water, the layers were separated and the aqueous phase was neutralized (pH = 7) with saturated aqueous Na_2CO_3 solution. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated to give a brown solid. The reaction was concentrated and the resulting residue purified on reverse-phase HPLC. LCMS *m/z* 381.3 (MH^+), t_R = 2.27 min.

Example 992.



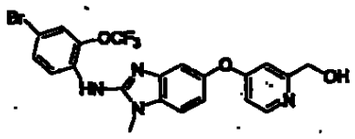
Synthesized as described in Example 1058 step 2 using 4-fluorophenylisiothiocyanate. LCMS *m/z* 365.4 (MH^+), t_R = 2.04 min.

Example 993



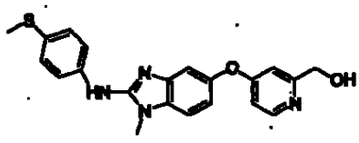
Synthesized as described in Example 991 step 2 using 4-bromo-3-methylphenylisiothiocyanate. LCMS *m/z* 439.3 (MH^+), t_R = 2.79 min.

Example 994



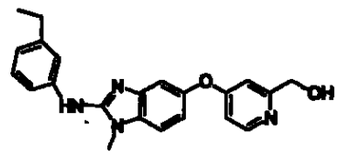
Synthesized as described in Example 991 step 2 using 4-bromo-2-trifluoromethoxyphenylisothiocyanate. LCMS *m/z* 511.3 (MH^+), t_R = 3.08 min.

Example 995



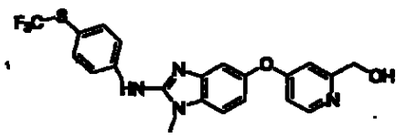
Synthesized as described in Example 991 step 2 using 4-methylthiophenylisiothiocyanate. LCMS *m/z* 393.4 (MH^+), t_R = 2.46 min.

Example 995



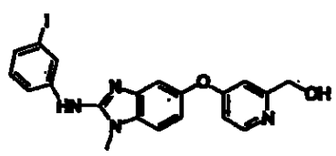
Synthesized as described in Example 991 step 2 using 3-ethylphenylisiothiocyanate. LCMS *m/z* 375.4 (MH^+), t_R = 2.57 min.

Example 996



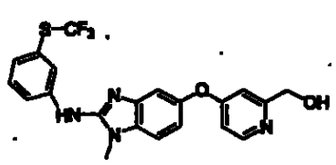
Synthesized as described in Example 991 step 2 using 4-trifluoromethylthiophenylisiothiocyanate. LCMS *m/z* 447.3 (MH^+), t_R = 3.21 min.

Example 997



Synthesized as described in Example 991 step 2 using 3-iodophenylisiothiocyanate. LCMS *m/z* 473.2 (MH^+), t_R = 2.57 min.

Example 998

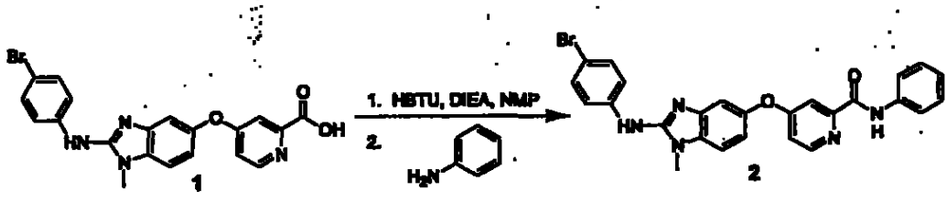


Synthesized as described in Example 991 step 2 using 3-trifluoromethylthiophenylisothiocyanate. LCMS *m/z* 447.3 (MH^+), t_R = 3.08 min.

Example 999: 4-[2-(4-Bromo-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid phenylamide.

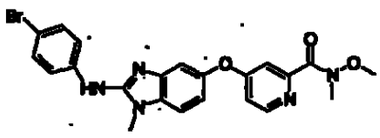
Procedure for Synthesis of Anilide Series (4-Br and 3-iPr west-ends)

Synthesis of 4-[2-(4-Bromo-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid phenylamide.



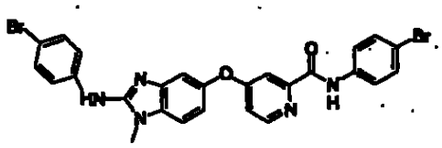
A suspension of 1 (44 mg, 0.1 mmol), HBTU (46 mg, 0.12 mmol), and DIEA (43 uL, 0.25 mmol) in NMP (0.5 mL) was shaken for 30 min at rt. Aniline was added and the reaction was shaken overnight. The crude product purified on reverse-phase HPLC. LCMS *m/z* 515.2 (MH^+), t_R = 2.75 min.

Example 1000



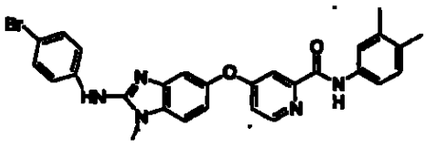
Synthesized as described in Example 999 using *N*, *O*-dimethylhydroxylamine HCl. LCMS *m/z* 483.3 (MH^+), t_R = 2.07 min.

Example 1001



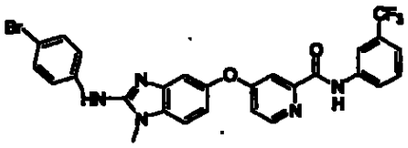
Synthesized as described in Example 999 using 4-bromoaniline. LCMS *m/z* 594.0 (MH^+), t_R = 5.39 min.

Example 1002



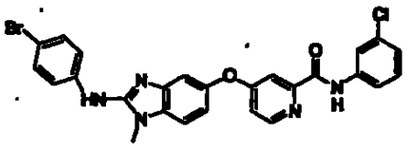
Synthesized as described in Example 999 using 3,4-dimethylaniline. LCMS *m/z* 543.2 (MH^+), t_R = 5.39 min.

Example 1003



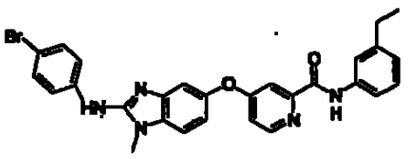
Synthesized as described in Example 999 using 3-trifluoromethylaniline. LCMS *m/z* 583.1 (MH^+), t_R = 3.12 min.

Example 1004



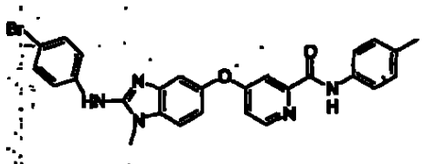
Synthesized as described in Example 999 using 3-chloroaniline. LCMS *m/z* 550.1 (MH^+), t_R = 5.28 min.

Example 1005



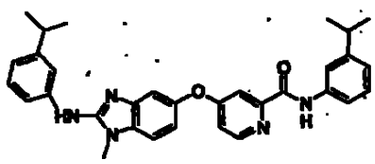
Synthesized as described in Example 999 using 3-ethylaniline. LCMS *m/z* 543.2 (MH^+), t_R = 3.16 min.

Example 1006



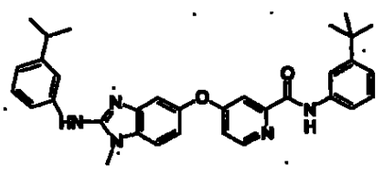
Synthesized as described in Example 1067 using 4-methylaniline. LCMS *m/z* 529.2 (MH^+), t_R = 5.15 min.

Example 1007



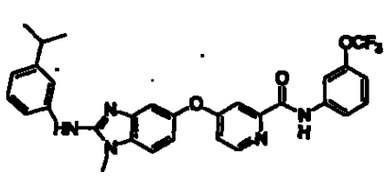
Synthesized as described in Example 999 using 3-isopropylaniline. LCMS *m/z* 520.3 (MH^+), t_R = 5.98 min.

Example 1008



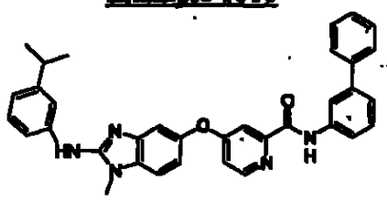
Synthesized as described in Example 999 using 3-tert-butylaniline. LCMS *m/z* 534.3 (MH^+), t_R = 3.32 min.

Example 1009



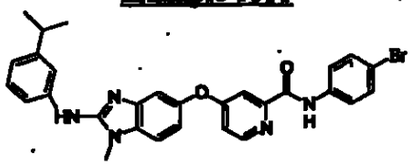
Synthesized as described in Example 999 using 3-trifluoromethoxyaniline. LCMS *m/z* 562.2 (MH^+), t_R = 3.15 min.

Example 1010



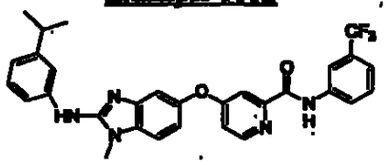
Synthesized as described in Example 999 using 3-biphenylamine. LCMS *m/z* 554.3 (MH^+), t_R = 3.28 min.

Example 1011



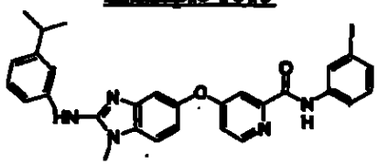
Synthesized as described in Example 999 using 4-bromoaniline. LCMS *m/z* 557.2 (MH^+), t_R = 5.65 min.

Example 1012



Synthesized as described in Example 999 using 3-trifluoromethylaniline. LCMS *m/z* 546.3 (MH^+), t_R = 5.74 min.

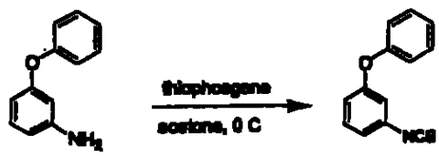
Example 1013



Synthesized as described above in Example 999 using 3-iodoaniline. LCMS *m/z* 604.2 (MH^+), t_R = 5.81 min.

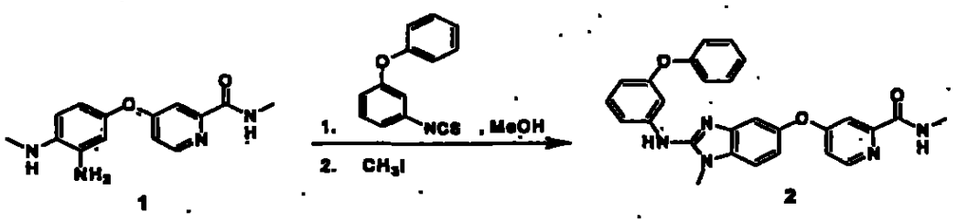
Example 1014: 4-[1-Methyl-2-(3-phenoxy-phenylamino)-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid methylamide

Step 1. Synthesis of 3-phenoxyphenylisothiocyanate



To a stirring solution of 3-phenoxyaniline (185 mg, 1.0 mmol) in acetone (4.0 mL) at 0°C was added thiophosgene (0.23 mL, 3.0 mmol) and the resulting reaction maintained for 30 min. The reaction determined complete by TLC (4 : 1 hexane/EtOAc). The reaction was concentrated, azeotroped with toluene and taken on without further purification.

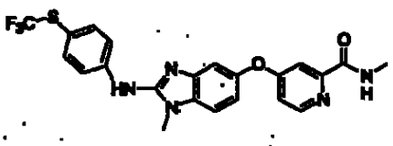
Step 2. Synthesis of 4-[1-Methyl-2-(3-phenoxy-phenylamino)-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid methylamide



1 2

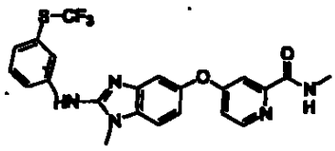
A 1 dram vial was charged with a solution of 3-phenoxyphenylisothiocyanate (23 mg, 0.1 mmol), diamine 1 (27 mg, 0.1 mmol), and MeOH (0.5 mL) and the reaction was shaken at rt overnight. Methyl iodide (8 uL, 0.13 mmol) was added and the mixture shaken overnight. The reaction was concentrated and the resulting residue purified on reverse phase HPLC. LCMS *m/z* 466.3 (MH^+), t_R = 2.40 min.

Example 1015



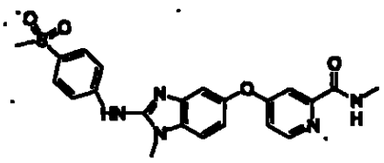
Synthesized as described in Example 1014 step 2 using 4-trifluoromethylthiophenylisothiocyanate. LCMS *m/z* 474.5 (MH^+), t_R = 3.76 min.

Example 1016



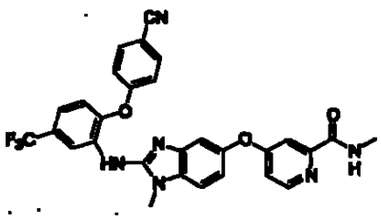
Synthesized as described in Example 1014 step 2 using 3-trifluoromethylthiophenylisothiocyanate. LCMS *m/z* 474.5 (MH^+), t_R = 3.65 min.

Example 1017



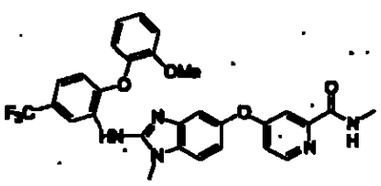
Synthesized as described in Example 1014 step 2 using 4-1-isothiocyanato-4-methanesulfonyl-benzene, prepared as in step 1. LCMS *m/z* 452.5 (MH^+), t_R = 2.86 min.

Example 1018



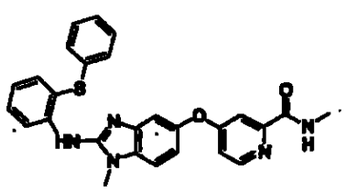
Synthesized as described in Example 1014 step 2 using 4-(2-isothiocyanato-4-trifluoromethyl-phenoxy)-benzonitrile, prepared as in step 1. LCMS *m/z* 559.6 (MH^+), t_R = 4.22 min.

Example 1019



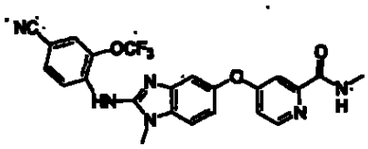
Synthesized as described in Example 1014 step 2 using 2-(2-methoxy-phenoxy)-5-trifluoromethyl-phenylisothiocyanate, prepared as in step 1. LCMS *m/z* 564.6 (MH^+), t_R = 4.42 min.

Example 1020.



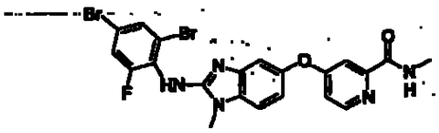
Synthesized as described in Example 1014 step 2 using 2-phenylsulfanyl-phenylisothiocyanate, prepared as in step 1. LCMS *m/z* 482.5 (MH^+), t_R = 3.85 min.

Example 1021.



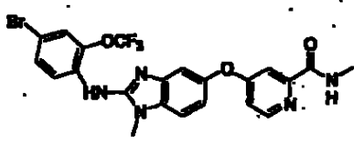
Synthesized as described in Example 1014 step 2 using 4-isothiocyanato-3-trifluoromethoxy-benzonitrile, prepared as in step 1. LCMS *m/z* 483.4 (MH^+), t_R = 2.35 min.

Example 1022.



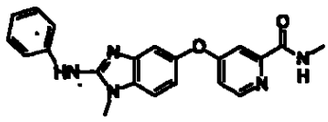
Synthesized as described in Example 1014 step 2 using 2,4-dibromo-6-fluorophenylisothiocyanate. LCMS *m/z* 550.3 (MH^+), t_R = 3.50 min.

Example 1023.



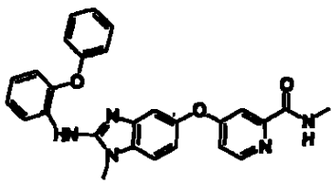
Synthesized as described in Example 1014 step 2 using 4-bromo-2-trifluoromethoxy-phenylisothiocyanate. LCMS *m/z* 537.3 (MH^+), t_R = 3.89 min.

Example 1024.



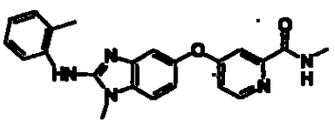
Synthesized as described in Example 1014 step 2 using phenylisothiocyanate. LCMS *m/z* 374.5 (MH^+), t_R = 2.84 min.

Example 1025.



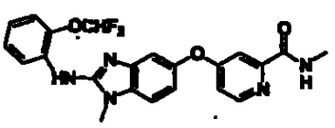
Synthesized as described in Example 1014 step 2 using 2-phenoxy-phenylisothiocyanate, prepared as in step 1. LCMS *m/z* 466.5 (MH^+), t_R = 2.37 min.

Example 1026.



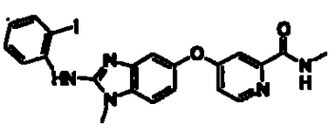
Synthesized as described in Example 1014 step 2 using 2-methyl-phenylisothiocyanate. LCMS *m/z* 388.5 (MH^+), t_R = 2.99 min.

Example 1027.



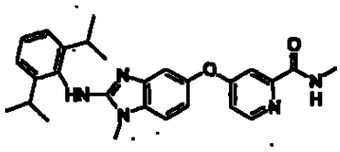
Synthesized as described in Example 1014 step 2 using 2-difluoromethoxy-phenylisothiocyanate. LCMS *m/z* 440.5 (MH^+), t_R = 3.13 min.

Example 1028.



Synthesized as described in Example 1014 step 2 using 2-iodo-phenylisothiocyanate. LCMS *m/z* 500.4 (MH^+), t_R = 2.07 min.

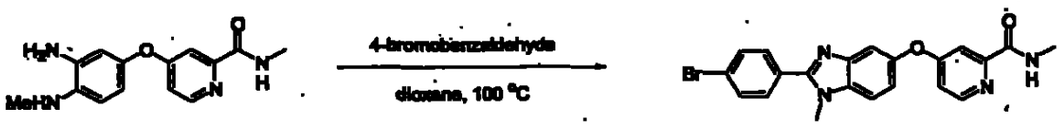
Example 1029.



Synthesized as described in Example 1014 step 2 using 2,6-diisopropyl-phenylisothiocyanate. LCMS *m/z* 430.5 (MH^+), t_R = 2.27 min.

Example 1030.

4-[2-(4-Bromophenyl)-1-methyl-1H-benzimidazol-5-yloxy]-pyridine-2-carboxylic acid methylamide.

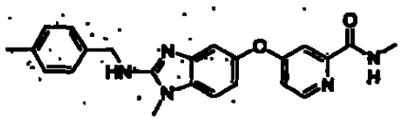


1 2

A mixture of diamine 1 (137 mg, 0.36 mmol) and 4-bromobenzaldehyde (66 mg, 0.50 mmol) in dry dioxane (2 mL) was heated to 100 °C for 16 h. The reaction mixture was allowed to cool to rt and was then concentrated. The resulting residue was purified by reverse phase HPLC to furnish 2 as the TFA salt: LCMS *m/z* 437.1, t_R = 2.16 min.

Example 1031

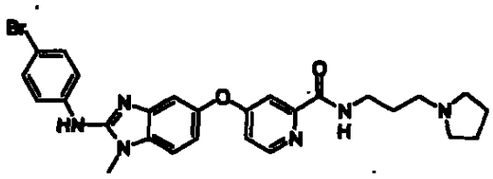
4-[1-Methyl-2-(4-methylbenzylamino)-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid methylamide.



Prepared as per Example 120b using 4-methylbenzyl thioisocyanate: LCMS *m/z* 402.2 (MH^+), t_R = 1.91 min.

Example 1032

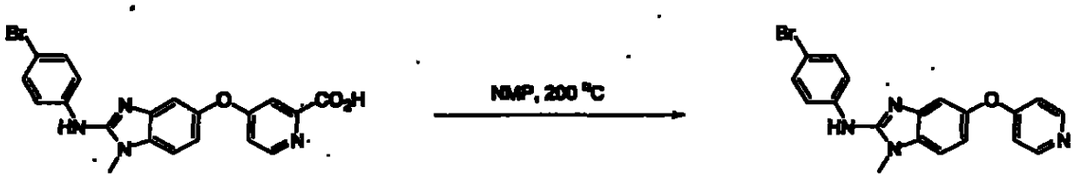
4-[2-(4-Bromophenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide.



Prepared as per Example 371 using amido-1-(3-aminopropyl)pyrrolidine: LCMS *m/z* 549.5 (MH^+), t_R = 2.97 min.

Example 1033.

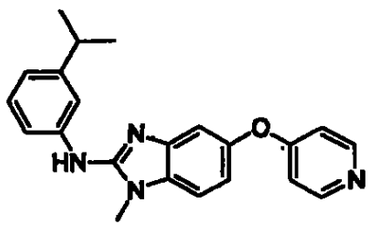
(4-Bromophenyl)-[1-methyl-5-(pyridin-4-yloxy)-1H-benzolimidazol-2-yl]-amine



1 2

A solution of acid 1 (44 mg, 0.1 mmol) in dry NMP (1 mL) was heated at 200 °C for 20 min. The reaction was allowed to cool to rt and the crude reaction mixture was directly purified on reverse-phase HPLC to provide 2 as a TFA salt: ^1H NMR (300 MHz, CD3OD) δ 8.67 (d, *J* = 7.4 Hz, 2 H), 7.70 (d, *J* = 8.5 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 7.42 (d, *J* = 7.4 Hz, 2 H), 7.32 (d, *J* = 2.2 Hz, 1 H), 7.26 (dd, *J* = 2.2, 8.5 Hz, 1 H), 3.86 (s, 3 H); LCMS m/z 395.0 (MH^+), t_R = 1.48 min.

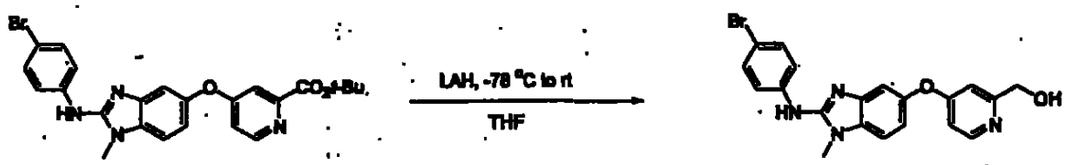
Example 1034



LCMS *m/z* 359.3 (MH^+), t_R = 1.91 min.

Example 1035

{4-[2-(4-Bromophenylamino)-1-methyl-1H-benzolimidazol-5-yloxy]-pyridin-2-yl}-methanol



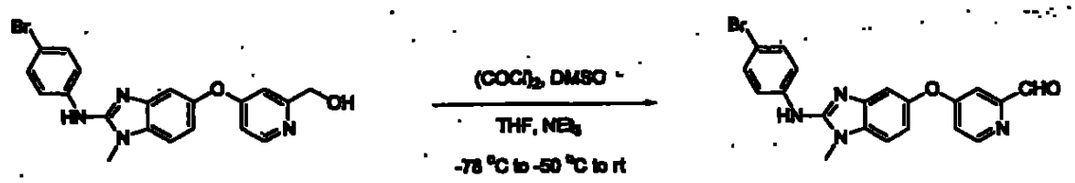
1 2

A suspension of *t*-butyl ester 1 (496 mg, 1.0 mmol) in dry THF (3 mL) was added to a stirring suspension of LAH (61 mg, 1.6 mmol) in dry THF (2 mL) at –78°C. The reaction was allowed to warm to rt over 3 h. After the reaction was judged complete by LCMS, water (30 ul, 1.7 mmol) and NaF (270 mg, 6.4 mmol) were added and the resulting mixture was stirred vigorously overnight at rt. The crude mixture was filtered through Celite and the remaining solids were rinsed with EtOAc. The combined organic portions were concentrated and a portion of the resulting residue was purified by reverse-phase HPLC to furnish alcohol 2 as a TFA salt: ^{1}H NMR (300 MHz, CD3OD) δ 8.56 (d, J = 7.2 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.69 (d, J = 8.8 Hz, 2 H), 7.45 (d, J = 8.8 Hz, 2 H), 7.33 (m, 3 H), 7.28 (dd, J = 2.2, 8.5 Hz, 1 H), 4.86 (app s, 2 H), 3.87 (s, 3 H); LCMS *m/z* 425.1, t_R = 1.49 min.

Example 1036: (4-Bromophenyl)-[1-methyl-5-(2-methylaminomethyl-pyridin-4-yloxy)-1H benzoimidazol-2-yl]-amine

General Preparation for Benzyl Amines

Step 1. 4-[2-(4-Bromophenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxaldehyde

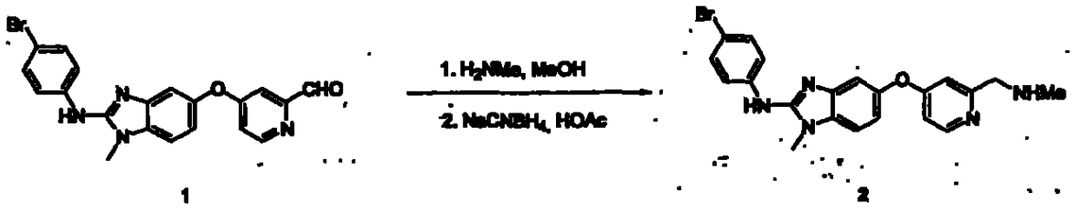


1 2

Dry DMSO (0.1 mL, 1.4 mmol) was added to a solution of oxalyl chloride (0.11 mL, 1.3 mmol) in dry THF (2 mL) at –78 °C and the resulting solution was maintained at –78 °C for 30 min. A solution of alcohol 1 in dry THF (2 mL) was then introduced and the resulting reaction was maintained at –78 °C for 30 min, then at –50 °C for 45 min.

Triethylamine (0.5 mL, 3.6 mmol) was added and the reaction was allowed to warm to rt over 1 h. The reaction was quenched with water and partitioned with EtOAc. The layers were separated and the aqueous portion was extracted with EtOAc (3 X). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The resulting residue was carried forward without further purification.

Step 2. (4-Bromophenyl)-[1-methyl-5-(2-methylaminomethyl-pyridin-4-yloxy)-1H benzoimidazol-2-yl]-amine.

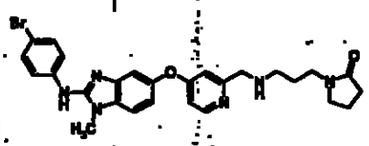
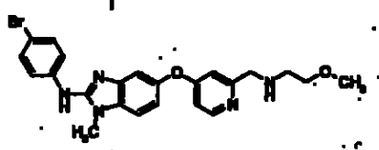
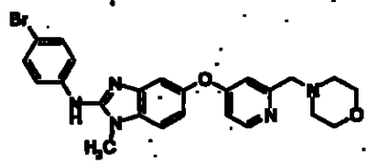
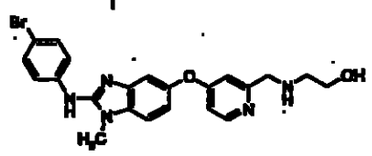
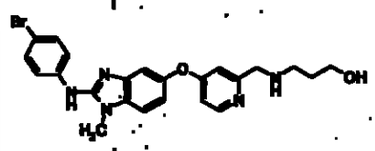
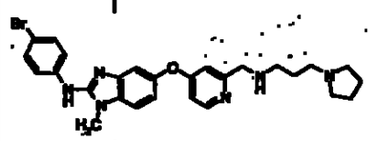
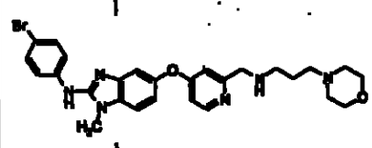


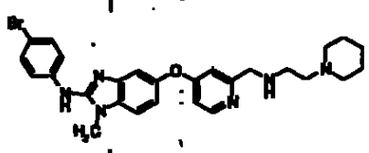
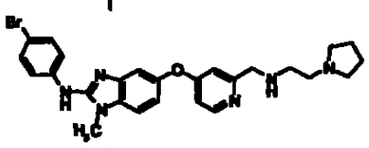
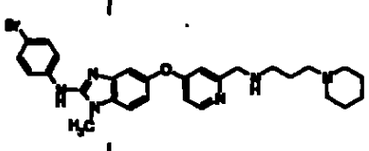
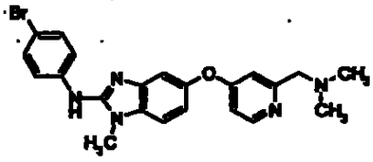
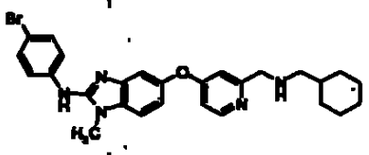
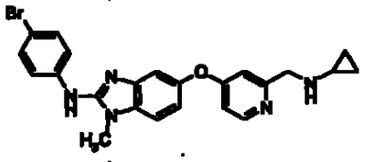
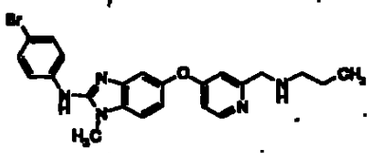
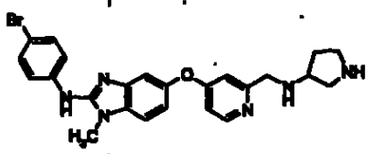
1 2

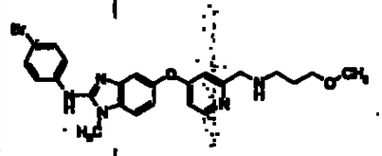
Methyl amine (0.3 mL, 0.6 mmol, 2.0 M in MeOH) was added to a solution of aldehyde 1 in MeOH (1 mL) and the reaction was maintained at rt for 2 d. The reaction was acidified by addition of acetic acid (pH = 3-4), and an excess of $NaBH_3CN$ was added. The reaction was maintained for 2 d then concentrated. The crude reaction mixture was dissolved in EtOAc and partitioned with aqueous saturated NaHCO3 solution. The layers were separated and the aqueous phase was extracted with EtOAc (3 X). The combined organic portions were washed with brine, dried ($MgSO_4$), and concentrated. The resulting residue was purified by reverse-phase HPLC to afford *N*-methyl amine 2 as a TFA salt: ^{1}H NMR (300 MHz, CD_3OD) δ 8.48 (d, J = 5.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2 H), 7.67 (d, J = 9.4 Hz, 1 H), 7.43 (d, J = 8.8 Hz, 2 h), 7.20 (dd, J = 2.2, 9.4 Hz, 1 H), 7.19 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 2.2, 1 H), 6.90 (dd, J = 2.2, 5.8 Hz, 1 H), 4.27 (s, 2 H), 3.86 (s, 3 H), 2.76 (s, 3 H); LCMS *m/z* 438.5 (MH^+), t_R = 1.85 min.

The following tabulated benzyl amines were prepared by the above method as in Example 1036 using the appropriate amine.

Table 14

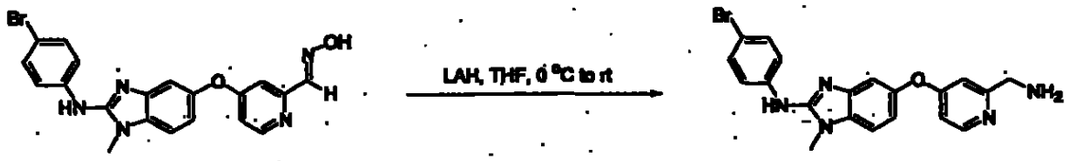
Example	Structure	LCMS (MH^+) *m/z*	TIME t_R (min)
		549.1	1.62
		482.2	1.94
		494.1	1.59
		468.2	1.87
		483.3	1.83
		536.2	1.87
		552.2	1.84

Example	Structure	LCMS (MH^+) *m/z*	TIME t_R (min)
		536.4	1.80
		522.3	1.76
		550.4	1.80
		452.3	2.70*
		521.4	3.63*
		465.3	2.75*
		467.3	2.86*
		494.2	1.82

Example	Structure	LCMS (MH^+) *m/z*	TIME t_R (min)
		497.2	2.04

Example 1053

[5-(2-Aminomethyl-pyridin-4-yloxy)-1-methyl-1H-benzoimidazol-2-yl]-(4-bromophenyl)-amine.

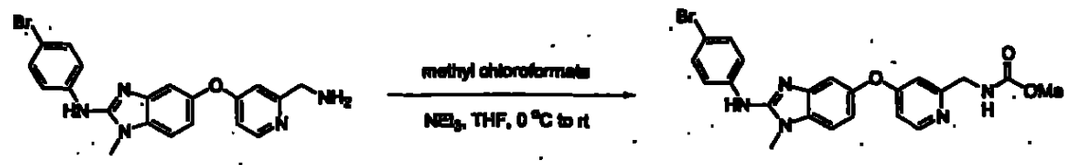


1 2

LAH (98 mg, 2.5 mmol) was added portionwise to a stirring solution of oxime 1 (225 mg, 0.5 mmol) in dry THF (3 mL) at 0 °C. After addition, the cooling bath was removed and the reaction was allowed to warm to rt overnight. The reaction was quenched by addition of water (0.1 mL), 10% w/w aqueous NaOH solution (0.1 mL), and water (0.3 mL). The resulting slurry was stirred at rt for 1 h and filtered through Celite. The remaining solids were rinsed with EtOAc and the organic portions were combined and concentrated. The crude residue was purified by reverse-phase HPLC to provide benzyl amine 2 as a TFA salt: LCMS *m/z* 424.1 (MH^+), t_R = 1.87 min.

Example 1054

{4-[2-(4-Bromophenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridin-2-yl-methyl]-carbamic acid methyl ester.

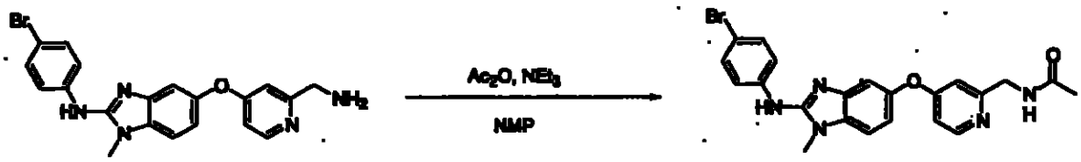


1 2

Methyl chloroformate (6 μL, 0.08 mmol) was added to a solution of benzyl amine 1 (21 mg, 0.05 mmol) and triethylamine (69 μL, 0.5 mmol) in dry THF (1 mL) at 0 °C. The reaction was maintained at 0°C for 20 min, then at rt for 2 h. The reaction mixture was concentrated and purified by reverse-phase HPLC to provide methyl carbamate 2 as a TFA salt: LCMS *m/z* 482.2 (MH^+), t_R = 1.96 min.

Example 1055

N-{4-[2-(4-Bromophenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridin-2-ylmethyl}acetamide.



1 2

To a solution of benzyl amine 1 (17 mg, 0.04 mmol) in dry NMP (2 mL) was added triethylamine (0.06 mL, 0.4 mmol) and acetic anhydride (0.04 mL, 0.4 mmol). The resulting reaction was maintained at rt overnight and purified directly by reverse-phase HPLC to furnish acetamide 2 as a TFA salt: LCMS *m/z* 466.3 (MH^+), t_R = 1.78 min.

Example 1056: 4-[2-(3-Ethylphenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid [3-(2-oxo-pyrrolidin-yl)-propyl]-amide.

General Preparation for N-(3-Aminopropyl)-pyrrolidinone Amides

Step 1: 4-Chloro-pyridine-2-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

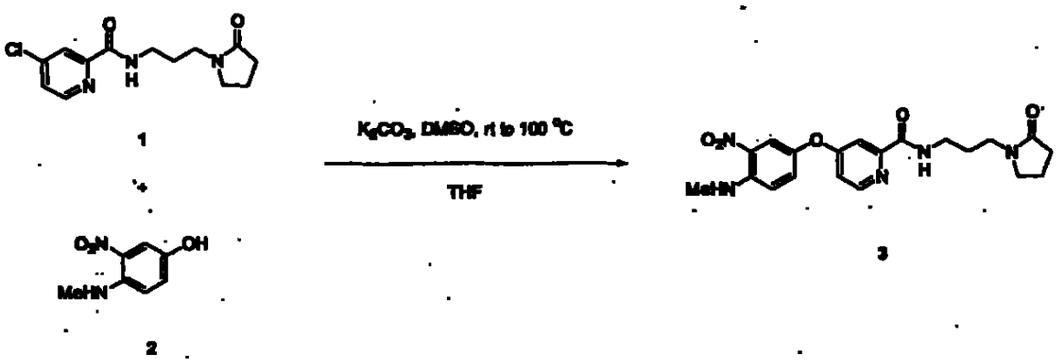


1 2 3

Acid chloride 1 (2.12 g, 10 mmol) was treated with N-methylmorpholine (4.5 mL, 41 mmol) and *N*-(3-aminopropyl)-pyrrolidinone 2 (1.6 mL, 11 mmol) in dry THF (40 mL). The reaction was maintained overnight and concentrated. The residue was

dissolved in EtOAc and partitioned with water. The aqueous portion was extracted with EtOAc (3 X) and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by Kugelrohr distillation (0.5 mmHg, 170-200°C) to provide 3.

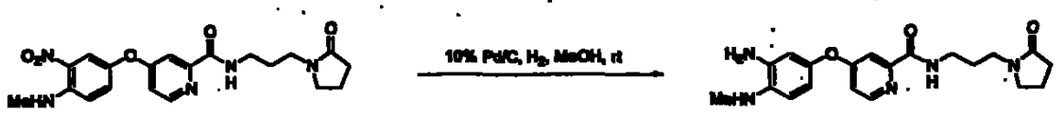
Step 2: 4-(4-Methylamino-3-nitrophenoxy)-pyridine-2-carboxylic acid [3-(2-oxo-pyrrolidin-yl)-propyl]-amide



1 + 2 → 3

Prepared as per Example 120b with the appropriate substitutions. Amide 3 can be purified by flash chromatography (95:5 CH_2Cl_2-MeOH). It can also be further purified by recrystallization from MeCN.

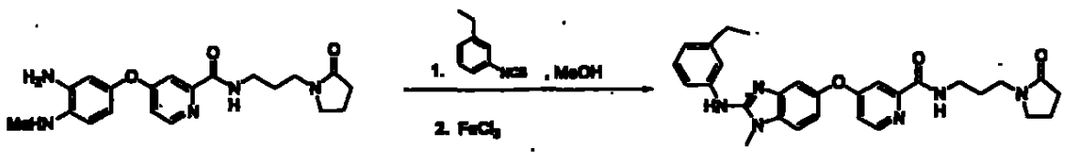
Step 3: 4-(3-Amino-4-methylamino-phenoxy)-pyridine-2-carboxlic acid [3-(2-oxo-pyrrolidin-yl)-propyl]-amide



1 → 2

Prepared as per Example 120b .

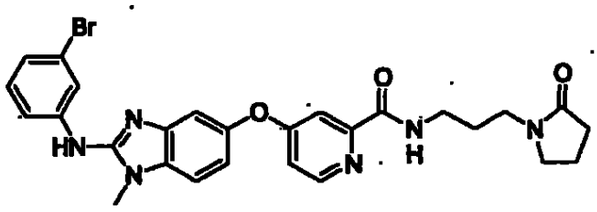
Step 4: 4-[2-(3-Ethylphenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pryidine-2-carboxylic acid [3-(2-oxo-pyrrolidin-yl)-propyl]-amide.



1 2

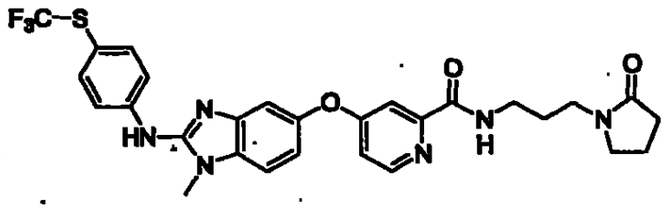
Prepared as per Example 120b to provide benzimidazole 2 as a TFA salt: LCMS *m/z* 513.3 (MH^+), t_R = 2.22 min.

Example 1057



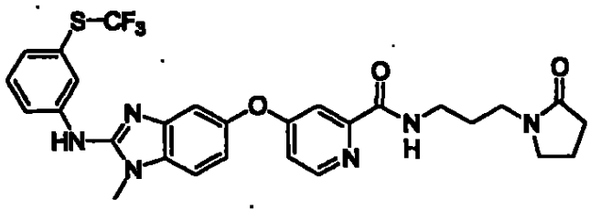
Prepared as per Example 1056: LCMS *m/z* 563.2 (MH^+), t_R = 2.15 min.

Example 1058



Prepared as per Example 1056: LCMS t_R = 585.3 (MH^+), t_R = 2.55 min.

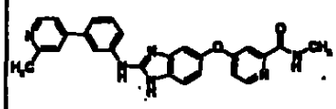
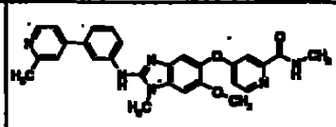
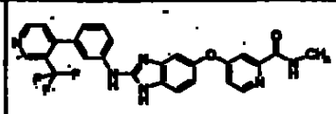
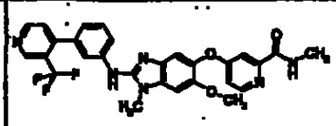
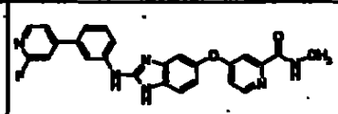
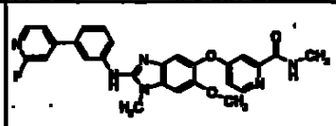
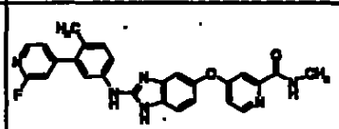
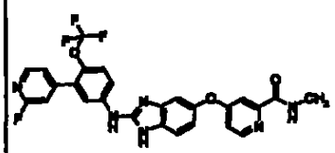
Example 1059

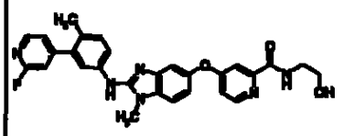
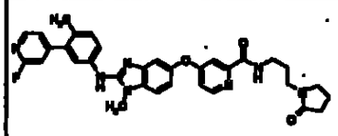
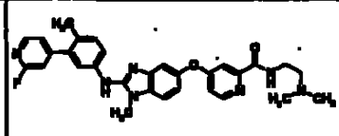
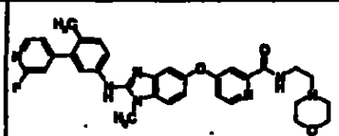
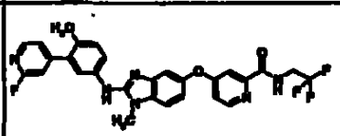
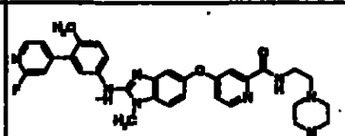
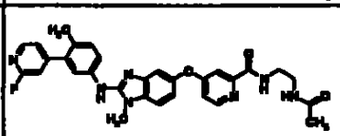
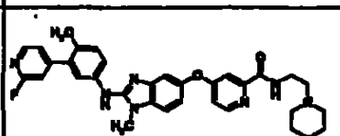


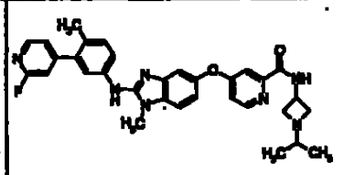
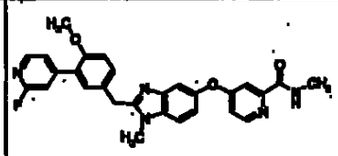
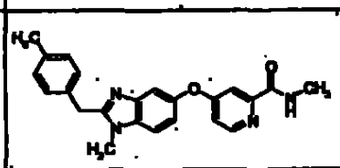
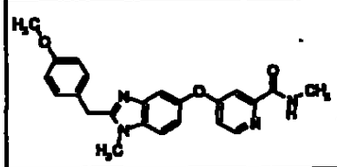
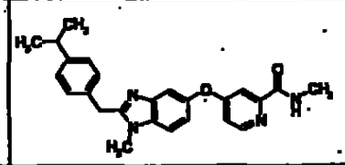
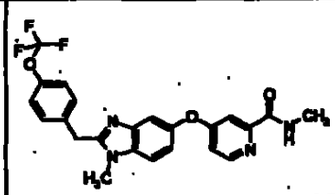
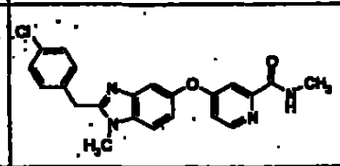
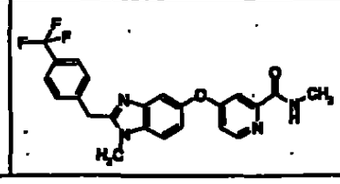
Prepared as per Example 1056: LCMS *m/z* 563.2 (MH^+), t_R = 2.50 min.

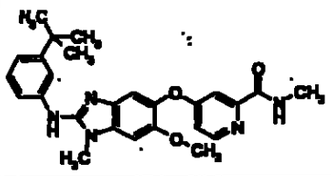
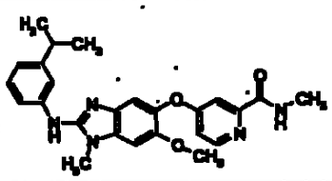
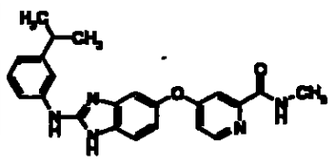
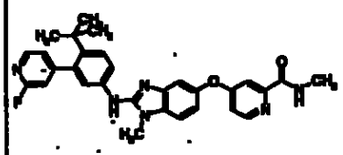
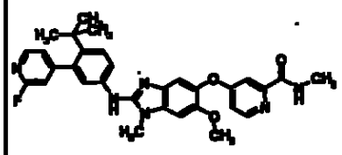
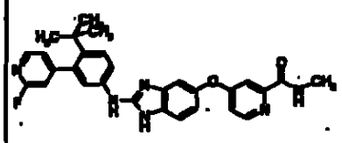
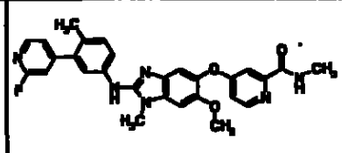
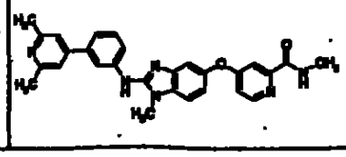
The following additional compounds were prepared following the procedures of the indicated Examples:

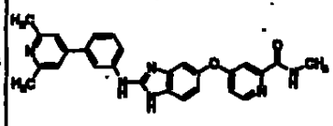
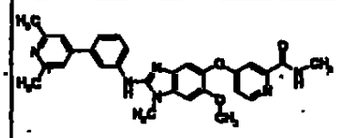
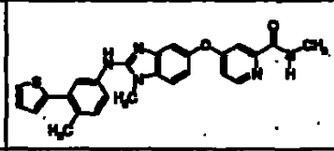
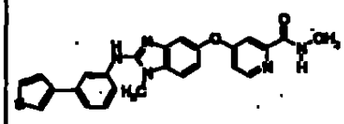
Table 15

Example	Structure	Name	MH+	Synthesized as in Ex.:
1060		N-methyl-4-[(2-{[3-(2-methyl-pyridin-4-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	451.5	702
1061		N-methyl-4-[(1-methyl-6-(methyloxy)-2-{[3-(2-methyl-pyridin-4-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	495.6	702
1062		N-methyl-4-{[2-({3-[3-(trifluoromethyl)pyridin-4-yl]-phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridine-2-carboxamide	505.5	702
1063		N-methyl-4-{[1-methyl-6-(methyloxy)-2-({3-[3-(trifluoromethyl)pyridin-4-yl]phenyl}-amino)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	549.5	702
1064		4-[(2-{[3-(2-fluoropyridin-4-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	455.5	702
1065		4-{[2-{[3-(2-fluoropyridin-4-yl)phenyl]amino}-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	499.5	702
1066		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	469.5	702
1067		4-{[2-({3-(2-fluoropyridin-4-yl)-4-[(trifluoromethyl)oxy]-phenyl}amino)-1H-benzimidazol-5-yl]oxy}-N-methyl-pyridine-2-carboxamide	539.5	702

Example	Structure	Name	MH+	Synthesized as in Ex.:
1068		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-(2-hydroxyethyl)-pyridine-2-carboxamide	513.5	483
1069		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-[3-(2-oxopyrrolidin-1-yl)propyl]pyridine-2-carboxamide	594.7	483
1070		N-[2-(dimethylamino)ethyl]-4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	540.6	483
1071		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-(2-morpholin-4-ylethyl)-pyridine-2-carboxamide	582.6	483
1072		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-(2,2,2-trifluoroethyl)-pyridine-2-carboxamide	551.5	483
1073		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-(2-piperazin-1-ylethyl)-pyridine-2-carboxamide	581.7	483
1074		N-[2-(acetylamino)ethyl]-4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	554.6	483
1075		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-(2-piperidin-1-ylethyl)-pyridine-2-carboxamide	580.7	483

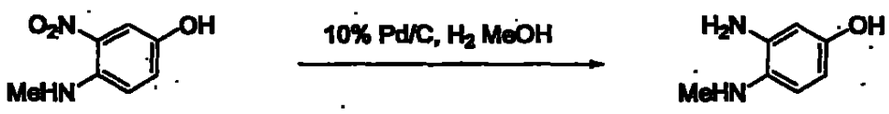
Example	Structure	Name	MH+	Synthesized as in Ex.:
1076		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-[1-(1-methylethyl)-azetidin-3-yl]pyridine-2-carbox-amide	566.7	636
1077		4-[(2-{[3-(2-fluoropyridin-4-yl)-4-(methyloxy)phenyl]methyl}-1-methyl-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	498.5	636
1078		N-methyl-4-({1-methyl-2-[(4-methylphenyl)methyl]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	387.5	636
1079		N-methyl-4-[(1-methyl-2-{[4-(methyloxy)phenyl]methyl}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide	403.5	636
1080		N-methyl-4-[(1-methyl-2-{[4-(1-methylethyl)phenyl]methyl}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	415.5	636
1081		N-methyl-4-{[1-methyl-2-({4-[(trifluoromethyl)oxy]phenyl}methyl)-1H-benzimidazol-5-yl]-oxy}pyridine-2-carboxamide	457.4	636
1082		4-({2-[(4-chlorophenyl)methyl]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide	407.9	636
1083		N-methyl-4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]methyl}-1H-benzimidazol-5-yl)oxy]-pyridine-2-carboxamide	441.4	636

Example	Structure	Name	MH+	Synthesized as in Ex.:
1084		4-{[2-{[3-(1,1-dimethylethyl)-phenyl]amino}-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	460.5	703
1085		N-methyl-4-{[1-methyl-2-{[3-(1-methylethyl)phenyl]amino}-6-(methyloxy)-1H-benz-imidazol-5-yl]oxy}pyridine-2-carboxamide	446.5	703
1086		N-methyl-4-[(2-{[3-(1-methyl-ethyl)phenyl]amino}-1H-benz-imidazol-5-yl)oxy]pyridine-2-carboxamide	402.5	1
1087		4-[(2-{[4-(1,1-dimethylethyl)-3-(2-fluoropyridin-4-yl)phenyl]-amino}-1-methyl-1H-benz-imidazol-5-yl)oxy]-N-methyl-pyridine-2-carboxamide	525.6	702
1088		4-{[2-{[4-(1,1-dimethylethyl)-3-(2-fluoropyridin-4-yl)phenyl]-amino}-1-methyl-6-(methyl-oxy)-1H-benzimidazol-5-yl]-oxy}-N-methylpyridine-2-carboxamide	555.6	702
1089		4-[(2-{[4-(1,1-dimethylethyl)-3-(2-fluoropyridin-4-yl)phenyl]-amino}-1H-benzimidazol-5-yl)-oxy]-N-methylpyridine-2-carboxamide	511.6	702
1090		4-{[2-{[3-(2-fluoropyridin-4-yl)-4-methylphenyl]amino}-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	513.5	702
1091		4-[(2-{[3-(2,6-dimethylpyridin-4-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	479.6	702

Example	Structure	Name	MH+	Synthesized as in Ex.:
1092		4-[(2-{[3-(2,6-dimethylpyridin-4-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide	465.5	702
1093		4-{[2-{[3-(2,6-dimethylpyridin-4-yl)phenyl]amino}-1-methyl-6-(methyloxy)-1H-benzimidazol-5-yl]oxy}-N-methylpyridine-2-carboxamide	509.6	702
1094a		N-methyl-4-({1-methyl-2-[(4-methyl-3-thien-2-ylphenyl)-amino]-1H-benzimidazol-5-yl}-oxy)pyridine-2-carboxamide	470.6	702
1094b		N-methyl-4-({1-methyl-2-[(3-thien-3-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)-pyridine-2-carboxamide	456.5	702

General Preparation for Phenolic Benzimidazoles

3-Amino-4-methylaminophenol

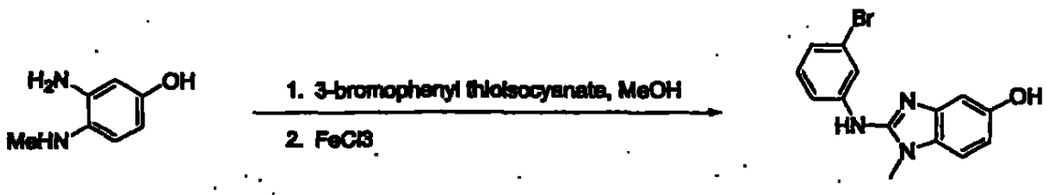


1 2

Diamine 2 prepared as per Example 120b from nitroaniline 1.

Example 1095

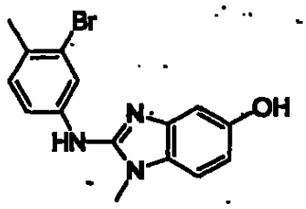
2-(3-Bromophenylamino)-1-methyl-1H-benzoimidazol-5-ol



1 2

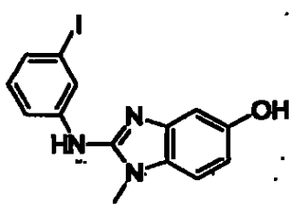
Benzimidazole 2 was prepared as per Example 120b: LCMS *m/z* 318.1 (MH^+), t_R = 2.07 min.

Example 1096



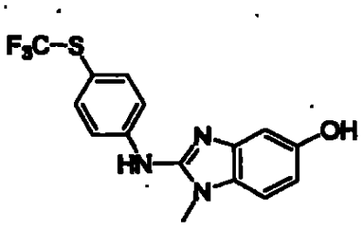
LCMS *m/z* 332.1 (MH^+), t_R = 2.22 min

Example 1097



LCMS *m/z* 366.1 (MH^+), t_R = 2.13 min

Example 1098

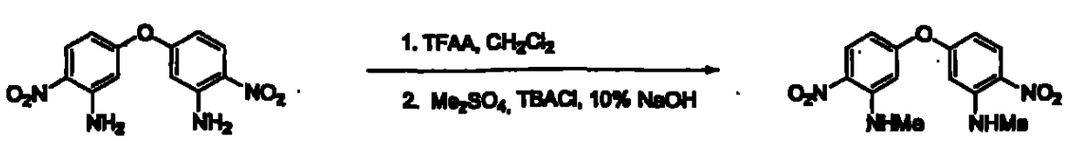


LCMS *m/z* 340.2 (MH^+), t_R = 2.39 min

Example 1099

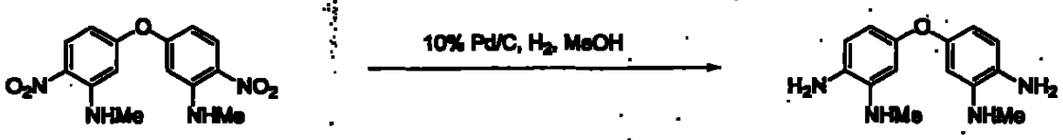
Preparation of Symmetrical bis-Benzimidazoles

Step 1: 4,4'-dimethylamino-3,3'-dinitro diphenyl ether



Diphenyl ether 2 was prepared using the method described in Example 120b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (br s, 2 H), 7.75 (d, J = 3.0 Hz, 2 H), 7.29 (app d, J = 3.0 Hz, 1 H), 6.87 (d, J = 9.5 Hz, 2 H), 3.05 (d, J = 5.2 Hz, 6 H).

Step 2: 4,4'-dimethylamino-3,3'-diamino diphenyl ether

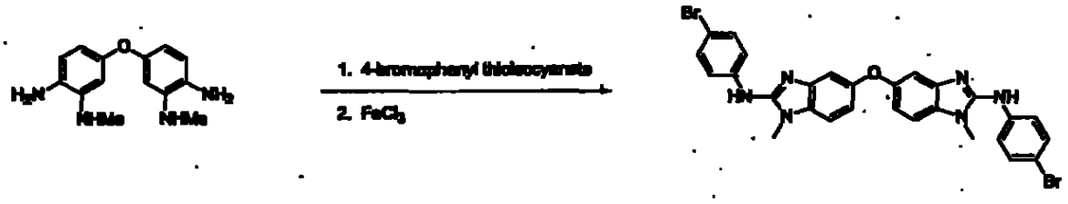


1 2

Tetramine 2 was prepared as per Example 120b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, J = 8.5 Hz, 2 H), 6.47 (dd, J = 2.8, 8.5 Hz, 2 H), 6.41 (d, J = 2.8 Hz, 2 H), 3.40 (br s, 4 H), 3.06 (br s, 2 H), 2.84 (d, J = 5.5 Hz, 6 H).

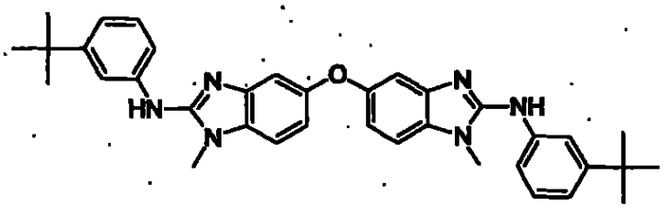
Example 1100

bis-5-[2-(3-Bromophenylamino)-1-methyl-1H-benzoimidazole]-ether.



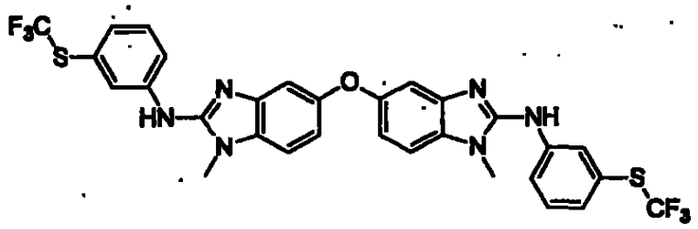
Prepared as per Example 120b: LCMS m/z 617.1 (MH^+), t_R = 2.27 min

Example 1101



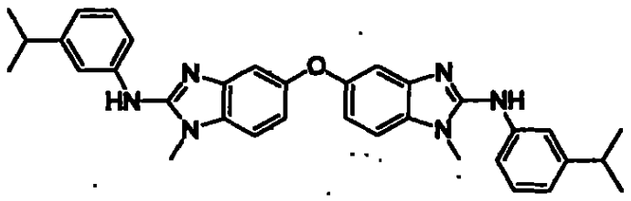
Prepared as per Example 120b: LCMS m/z 573.4 (MH^+), t_R = 2.78 min

Example 1102



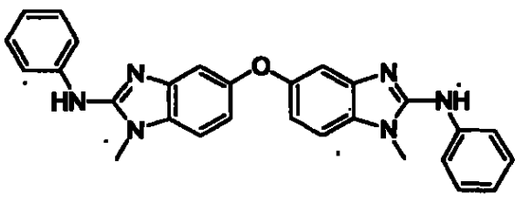
Prepared as per Example 120b: LCMS *m/z* 661.2 (MH^+), t_R = 2.83 min

Example 1103



Prepared as per Example 120b: LCMS *m/z* 545.4 (MH^+), t_R = 2.73 min

Example 1104

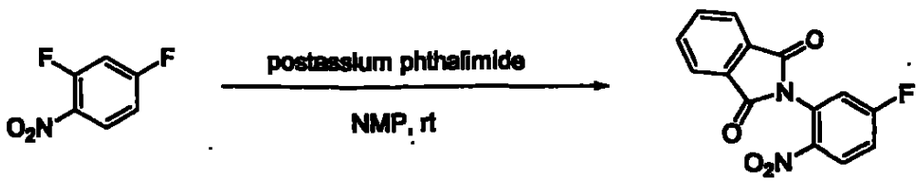


Prepared as per Example 120b: LCMS *m/z* 461.3 (MH^+), t_R = 1.98 min

Example 1105

Preparation of Benzo Derivatives

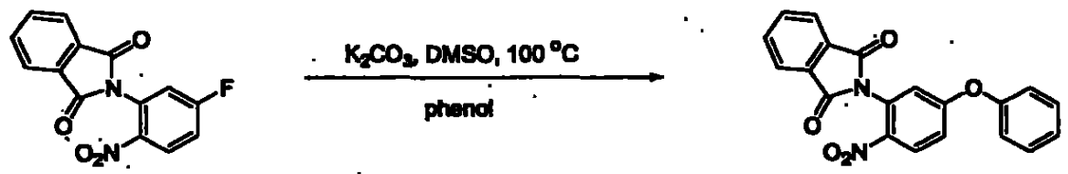
2-(N-Phthalimido)-4-fluoronitrobenzene



A suspension of 2,4 difluoronitrobenzene (15.9 g, 100 mmol) and postassium phthalimide (16.5 g, 100 mmol) was stirred in dry NMP (50 mL) for 3 d. The reaction solution was poured into MTBE and the resulting precipitate was collected by filtration. The solids were washed with MTBE (3 X) and the mother liquor was extracted with MTBE (3 X). The combined organic portions were washed with water (3 X) and concentrated to furnish a yellow solid which was combined with the initial crop of precipitate. The combined crude solid was purified by recrystallization from hot toluene, and the crystals were washed with cold MTBE: ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.31 (dd, J = 5.2, 9.1 Hz, 1 H), 7.98 (m, 4 H), 7.69 (dd, J = 2.8, 9.1 Hz, 1 H), 7.62 (ddd, J = 1.7, 2.8, 7.7 Hz, 1 H).

Example 1106

2-(N-Phthalimido)-4-phenoxynitrobenzene

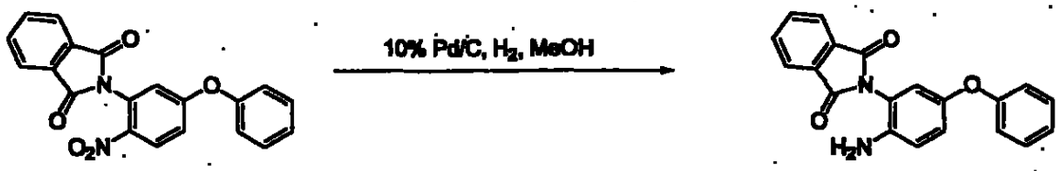


1 2

2-(N-Phthalimido)-4-phenoxynitrobenzene 2 was prepared using a similar procedure employed in Example 120b.

Example 1107

2-(N-Phthalimido)-4-phenoxyaniline

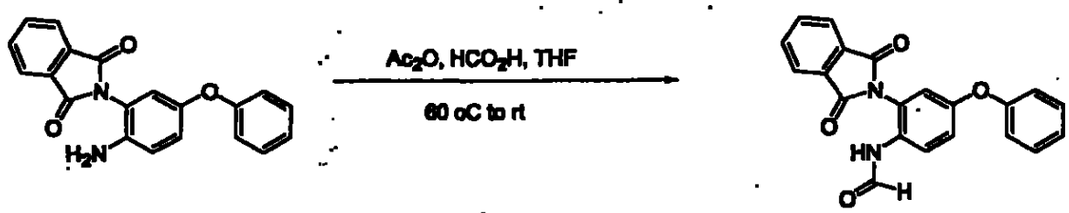


1 2

2-(N-Phthalimido)-4-phenoxyaniline 2 was obtained through the reduction of 2-(N-phthalimido)-4-phenoxynitrobenzene 1 as described in Example 120b.

Example 1108

N-[2-(N-Phthalimido)-4-phenoxy-phenyl]-formamide

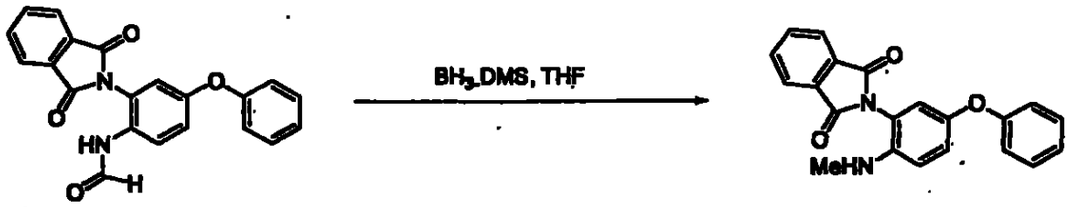


1 2

A mixture of formic acid (0.12 mL, 5.3 mmol) and acetic anhydride (0.24 mL, 2.5 mmol) was heated to 60 °C for 2 h. After allowing to cool to rt, a solution of aniline 1 (387 mg, 1.0 mmol) in dry THF (1 mL) was added and the reaction was maintained overnight. The reaction was concentrated and the resulting crude residue was directly used in the next step.

Example 1109

N-Methyl-[2-(N-phthalimido)-4-phenoxy]-aniline

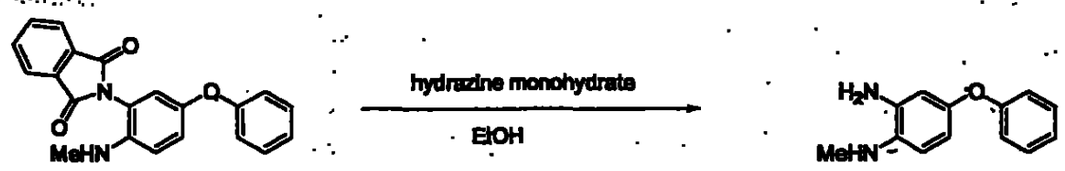


1 2

A solution of formamide 1 was treated with BH_3-DMS solution (2.0 M in CH_2Cl_2, 0.5 mL, 1.0 mL) and the reaction was allowed to warm to rt overnight. The reaction was concentrated and the resulting residue was dissolved in EtOAc. The solution was partitioned with saturated aqueous $NaHCO_3$ solution and the layers were separated. The aqueous phase was extracted with EtOAc (3 X) and the combined organics phases were washed with brine, dried ($MgSO_4$), adsorbed onto SiO_2 and purified by flash chromatography (4 : 1 hexanes-EtOAc) to furnish 2 as a colorless residue.

Example 1110

N1-Methyl-4-phenoxybenzene-1,2-diamine

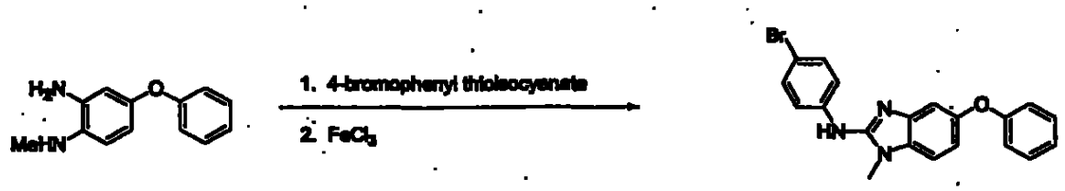


1 2

Hydrazine monohydrate (0.13 mL, 2.7 mmol) was added to a solution of phthalimide 1 (134 mg, 0.39 mmol) in ethanol (4 mL). The reaction was maintained overnight at rt and then was filtered through Celite. The filter cake was rinse with EtOAc (3 X) and the organic portions were combined and concentrated to give diamine 2 which was carried forward without further purification: LCMS *m/z* 215.1 (MH^+), t_R = 1.77 min.

Example 1111

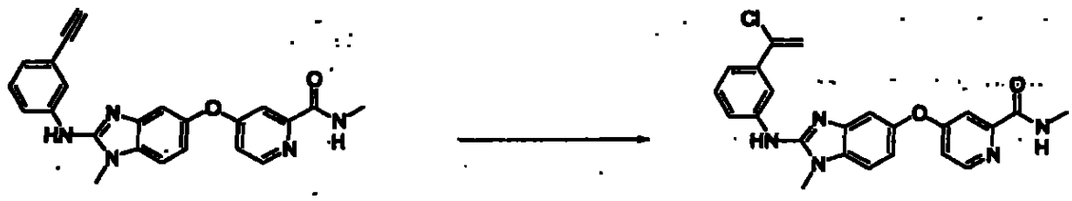
Synthesis of (4-Bromophenyl)-(1-methyl-5-phenoxy-1H-benzoimidazol-2-yl)-amine.



1 2

Benzimidazole 2 was prepared as per Example 120b: ^1H NMR (300 MHz, CD_3OD) δ 7.68 (app ddd, *J* = 2.9, 4.9, 8.8 Hz, 2 H), 7.53 (app d, *J* = 8.8 Hz, 1 H), 7.41 (app ddd, *J* = 2.9, 4.9, 8.8 Hz, 2 H), 7.40 (app ddd, *J* = 1.0, 2.0, 8.5 Hz, 2 h), 7.24 (app ddd, *J* = 1.0, 2.0, 8.5 Hz, 1 H), 7.07 (app dd, *J* =2.2, 8.8 Hz, 1 H), 7.00 (app d, *J* = 2.2 Hz, 1 H), 7.00 (app ddd, *J* = 1.0, 2.0, 8.5 Hz, 2 H), 3.82 (s, 3 H); LCMS *m/z* 394.0 (MH+), t_R = 2.36 min.

Example 1112

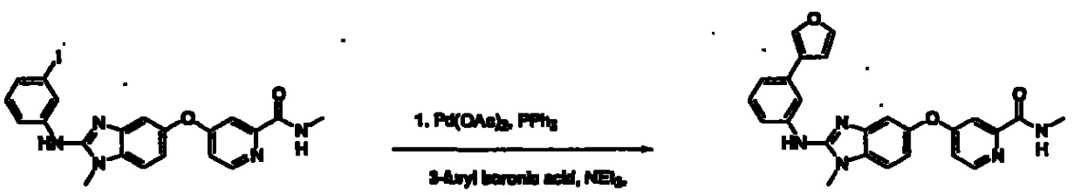


Example 371 1 2

A solution of 1 in MeCN was treated with aqueous 1 N HCl and freeze dried. The resulting residue was purified by reverse-phase HPLC to provide vinyl chloride 2 as a TFA salt: LCMS *m/z* 434.2 (MH^+), t_R = 2.48 min.

Example 1113

4-[2-(3-Furan-3-yl-phenylamino)-1-methyl-1H-benzoimidazol-5-yloxy]-pyridine-2-carboxylic acid methyl amide.

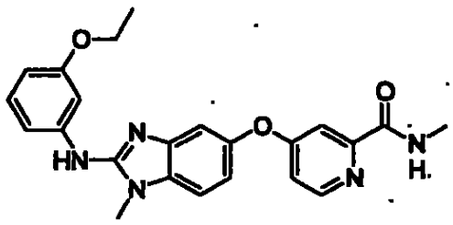


Example 311 1 2

A solution of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and triphenylphosphine (13.1 mg 0.05 mmol) in dry NMP (1 mL) was stirred at rt for 20 min. Aryl iodide 1 (100 mg, 0.2 mmol), 3-furyl boronic acid (45 mg, 0.4 mmol), and triethylamine (0.11 mL, 0.8 mmol) were added and the resulting solution was degassed and purged with Ar. The reaction was heated to 100°C for 2 h; LCMS indicated no conversion. The reaction was allowed to cool to rt under Ar and $Pd(dppf)Cl_2CH2Cl_2$ and diisopropylethylamine (0.14 mL) were added. The reaction was heated to 100 °C and maintained overnight. The reaction was allowed to cool to rt and LCMS indicated complete conversion. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and EtOAc and the resulting mixture filtered through Celite. The remaining solids were washed with water and EtOAc. The combined rinsings were partitioned and separated. The aqueous phase was extracted with EtOAc (3 X) and the combined organic portions were washed with

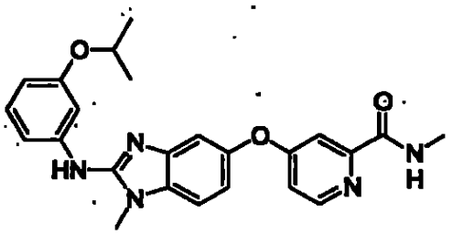
saturated aqueous Na_2CO_3, brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by reverse-phase HPLC to furnish 2 as a TFA salt: LCMS *m/z* 440.3 (MH^+), t_R = 2.35 min.

Example 1114



Prepared as per Example 120b.

Example 1115



Prepared as per Example 120b.

Example 1116

Raf/Mek Filtration Assay

Buffers

Assay buffer: 50 mM Tris, pH 7.5, 15 mM $MgCl_2$, 0.1 mM EDTA, 1 mM DTT

Wash buffer: 25 mM Hepes, pH 7.4, 50 mM sodium pyrophosphate, 500 mM NaCl

Stop reagent: 30 mM EDTA

Materials

Raf, active:	Upstate Biotech #14-352
Mek, inactive:	Upstate Biotech #14-205
^{33}P-ATP:	NEN Perkin Elmer #NEG 602 h
96 well assay plates:	Falcon U-bottom polypropylene plates #35-1190
Filter apparatus:	Millipore #MAVM 096 OR

96 well filtration plates: Millipore Immobilon 1 #MAIP NOB

Scintillation fluid: Wallac OptiPhase "SuperMix" #1200-439

Assay conditions

Raf approximately 120 pM

Mek approximately 60 nM

^{33}P-ATP 100 nM

Reaction time 45-60 minutes at room temperature

Assay protocol

Raf and Mek were combined at 2X final concentrations in assay buffer (50 mM Tris, pH 7.5, 15 mM $MgCl_2$. 0.1 mM EDTA and 1 mM DTT) and dispensed 15 µl per well in polypropylene assay plates (Falcon U-bottom polypropylene 96 well assay plates #35-1190. Background levels are determined in wells containing Mek and DMSO without Raf.

To the Raf/Mek containing wells was added 3 µl of 10X of a raf kinase inhibitor test compound diluted in 100% DMSO. The raf kinase activity reaction was started by the addition of 12 µl per well of 2.5X ^{33}P-ATP diluted in assay buffer. After 45-60 minutes, the reactions were stopped with the addition of 70 µl of stop reagent (30 mM EDTA). Filtration plates were pre-wetted for 5 min with 70% ethanol, and then rinsed by filtration with wash buffer. Samples (90 µl) from the reaction wells were then transferred to the filtration plates. The filtration plates were washed 6X with wash buffer using Millipore filtration apparatus. The plates were dried and 100 µl per well of scintillation fluid (Wallac OptiPhase "SuperMix" #1200-439) was added. The CPM is then determined using a Wallac Microbeta 1450 reader.

Example 1117

ASSAY 2: Biotinylated Raf Screen

In Vitro Raf Screen

The activity of various isoforms of Raf serine/threonine kinases can be measured by providing ATP, MEK substrate, and assaying the transfer of phosphate moiety to the MEK residue. Recombinant isoforms of Raf were obtained by purification from sf9

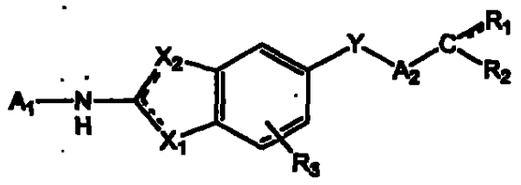
insect cells infected with a human Raf recombinant baculovirus expression vector. Recombinant kinase inactive MEK was expressed in *E. coli* and labeled with Biotin post purification. For each assay, test compounds were serially diluted in DMSO then mixed with Raf (0.50 nM) and kinase inactive biotin-MEK (50 nM) in reaction buffer plus ATP (1 uM). Reactions were subsequently incubated for 2 hours at room temperature and stopped by the addition of 0.5 M EDTA. Stopped reaction mixture was transferred to a neutradavin-coated plate (Pierce) and incubated for 1 hour. Phosphorylated product was measured with the DELFIA time-resolved fluorescence system (Wallac), using a rabbit anti-p-MEK (Cell Signaling) as the primary antibody and europium labeled anti-rabbit as the secondary antibody. Time resolved fluorescence was read on a Wallac 1232 DELFIA fluorometer. The concentration of each compound for 50% inhibition (IC_{50}) was calculated by non-linear regression using XL Fit data analysis software.

Using the procedures of Examples 1116 or 1117, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 5 μM.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of the formula (I):



(I)

wherein, X_1 and X_2 are independently selected from =N-, -NR_4-, -O- or –S-, provided that if X_1 is -NR_4-, -O- or –S-, then X_2 is =N-, or if X_2 is -NR_4-, -O- or –S-, then X_2 is =N-, and both X_1 and X_2 are not =N-; Y is O or S;

Y is O or S;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, heteroarylheteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, biarylalkyl, or heteroarylarylalkyl;

A_2 is substituted or unsubstituted heteroaryl;

R_1 is O or H, and R_2 is NR_5 R_6 or hydroxyl; or R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group; wherein, the dashed line represents a single or double bond;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen, hydroxyl, alkylamino, dialkylamino or alkyl;

R_5 and R_6 are independently selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl; or R_5 and R_6 are taken together to form substituted or unsubstituted heterocyclo or heteroaryl; and

the pharmaceutically acceptable salts, esters and prodrugs thereof.

2. A compound of Claim 1 wherein X is NR_4.

3. A compound of Claim 2 wherein R_4 is hydrogen.

4. A compound of Claim 2 wherein R_4 is methyl.

5. A compound of Claim 1 wherein Y is O.

6. A compound of Claim 1 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkylphenyl, chlorophenyl, flourophenyl, bromophenyl, iodophenyl, dihalophenyl, nitrophenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkylflourophenyl, triflouromethylchlorophenyl, triflouromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, triflourophenyl, (triflouromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-flouren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

7. A compound of Claim 1 wherein A_2 is substituted or unsubstituted pyridyl.

8. A compound of Claim 1 wherein R_1 is O and the dashed line represents a single or double bond.

9. A compound of Claim 1 wherein R_2 is NR_5R_6, R_5 is hydrogen and R_6 is selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl,

amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl.

10. A compound of Claim 1 wherein R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group.

11. A compound of Claim 1 wherein R_3 is loweralkoxy.

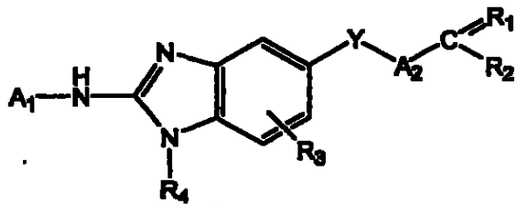
12. A compound of Claim 11 wherein R_3 is methoxy.

13. A compound of Claim 1 wherein R_4 is loweralkyl.

14. A compound of Claim 13 wherein R_4 is methyl.

15. The compound of claim 1 wherein R_1 is O, R_2 is NR_5R_6, R_5 is H, and R_6 is methyl.

16. A compound of the formula (II):



(II)

wherein and Y is O or S;

A_1 is substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, heteroarylheteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, biarylalkyl, heteroarylarylalkyl;

A_2 is substituted or unsubstituted heteroaryl;

R_1 is O and R_2 is NR_5 R_6; or R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group; wherein, the dashed line represents a single or double bond;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen or loweralkyl;

R_5 and R_6 are independently selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl; or R5 and R6 are taken together to form substituted or unsubstituted heterocyclo or heteroaryl; and

the pharmaceutically acceptable salts, esters, and prodrugs thereof.

17. A compound of Claim 16 wherein R4 is hydrogen.

18. A compound of Claim 16 wherein R4 is methyl.

19. A compound of Claim 16 wherein Y is O.

20. A compound of Claim 16 wherein A1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkylphenyl, chlorophenyl, flourophenyl, bromophenyl, iodophenyl, dihalophenyl, nitrophenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkylflourophenyl, triflouromethylchlorophenyl, triflouromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, triflourophenyl, (triflouromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-flouren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl,

hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

21. A compound of Claim 16 wherein A_2 is substituted or unsubstituted pyridyl.

22. A compound of Claim 16 wherein R_1 is O and the dashed line represents a single or double bond.

23. A compound of Claim 16 wherein R_2 is NR_5R_6, R_5 is hydrogen and R_6 is selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl.

24. A compound of Claim 16 wherein R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group.

25. A compound of claim 16 wherein R_1 is O, R_2 is NR_5R_6, R_5 is H, and R_6 is methyl.

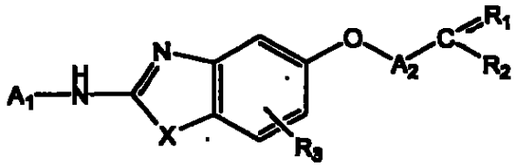
26. A compound of Claim 16 wherein R_3 is loweralkoxy.

27. A compound of Claim 26 wherein R_3 is methoxy.

28. A compound of Claim 16 wherein R_4 is loweralkyl.

29. A compound of Claim 28 wherein R_4 is methyl.

30. A compound of the formula (III):



(III)

wherein X is NR_4, O or S;

A_1 is substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, heteroarylheteroaryl,

cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, biarylalkyl, heteroarylarylalkyl;

A_2 is substituted or unsubstituted heteroaryl;

R_1 is O and R_2 is NR_5 R_6; or R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group; wherein, the dashed line represents a single or double bond;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen or loweralkyl;

R_5 and R_6 are independently selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl; or R5 and R6 are taken together to form substituted or unsubstituted heterocyclo or heteroaryl; and

the pharmaceutically acceptable salts, esters and prodrugs thereof.

31. A compound of Claim 30 wherein X is NR_4.

32. A compound of Claim 31 wherein R_4 is hydrogen.

33. A compound of Claim 30 wherein R_4 is methyl.

34. A compound of Claim 30 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkylphenyl, chlorophenyl, flourophenyl, bromophenyl, iodophenyl, dihalophenyl, nitrophenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkylflourophenyl, triflouromethylchlorophenyl, triflouromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, triflourophenyl, (triflouromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cyclqheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl,

hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-flouren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

35. A compound of Claim 30 wherein A_2 is substituted or unsubstituted pyridyl.

36. A compound of Claim 30 wherein R_1 is O and the dashed line represents a single or double bond.

37. A compound of Claim 30 wherein R_2 is NR_5R_6, R_5 is hydrogen and R_6 is selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl.

38. A compound of Claim 30 wherein R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group.

39. A compound of Claim 30 wherein R_3 is loweralkoxy.

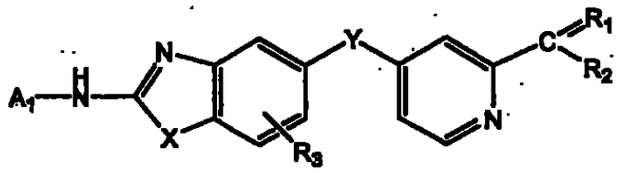
40. A compound of Claim 39 wherein R_3 is methoxy.

41. A compound of Claim 30 wherein R_4 is loweralkyl.

42. A compound of Claim 41 wherein R_4 is methyl.

43. A compound of claim 30 wherein R_1 is O, R_2 is NR_5R_6, R_5 is H, and R_6 is methyl.

44. A compound of the formula (IV):



(IV)

wherein X is NR_4, O or S;

Y is O or S;

A_1 is substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, heteroarylheteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, biarylalkyl, heteroarylarylalkyl;

R_1 is O and R_2 is NR_5 R_6; or R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group; wherein, the dashed line represents a single or double bond;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen or loweralkyl;

R_5 and R_6 are independently selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl; or R5 and R6 are taken together to form substituted or unsubstituted heterocyclo or heteroaryl; and

the pharmaceutically acceptable salts, esters and prodrugs thereof.

45. A compound of Claim 44 wherein X is NR_4.

46. A compound of Claim 45 wherein R_4 is hydrogen.

47. A compound of Claim 45 wherein R_4 is methyl.

48. A compound of Claim 44 wherein Y is O.

49. A compound of Claim 44 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkylphenyl, chlorophenyl, flourophenyl, bromophenyl, iodophenyl, dihalophenyl, nitrophenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl,

dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkylflourophenyl, trifluoromethylchlorophenyl, trifluoromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, trifluorophenyl, (trifluoromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceytl-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-flouren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

50. A compound of Claim 44 wherein R_1 is O and the dashed line represents a single or double bond.

51. A compound of Claim 44 wherein R_2 is NR_5R_6, R_5 is hydrogen and R_6 is selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl.

52. A compound of Claim 44 wherein R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group.

53. A compound of Claim 44 wherein R_3 is loweralkoxy.

54. A compound of Claim 53 wherein R_3 is methoxy.

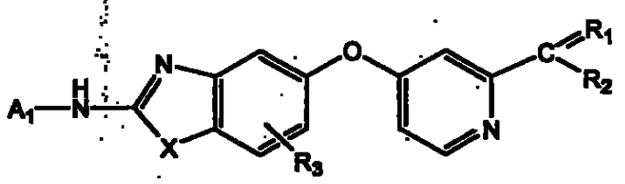
55. A compound of Claim 44 wherein R_4 is loweralkyl.

56. A compound of Claim 55 wherein R_4 is methyl.

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57. A compound of claim 44 wherein R_1 is O, R_2 is NR_5R_6, R_5 is H, and R_6 is methyl.

58. A compound of the formula (V):



(V)

wherein X is NR_4, O or S;

A_1 is substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, heteroarylheteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, biarylalkyl, heteroarylarylalkyl;

R_1 is O and R_2 is NR_5 R_6; or R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group; wherein, the dashed line represents a single or double bond;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen or loweralkyl;

R_5 and R_6 are independently selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl; or R5 and R6 are taken together to form substituted or unsubstituted heterocyclo or heteroaryl; and

the pharmaceutically acceptable salts, esters and prodrugs thereof.

59. A compound of Claim 58 wherein X is NR_4.

60. A compound of Claim 59 wherein R_4 is hydrogen.

61. A compound of Claim 59 wherein R_4 is methyl.

62. A compound of Claim 58 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl,

heterocyclylalkylphenyl, chlorophenyl, flourophenyl, bromophenyl, iodophenyl, dihalophenyl, nitrophenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkylflourophenyl, triflouromethylchlorophenyl, triflouromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, triflourophenyl, (triflouromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyi, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-flouren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

63. A compound of Claim 58 wherein R_1 is O and the dashed line represents a single or double bond.

64. A compound of Claim 58 wherein R_2 is NR_5R_6, R_5 is hydrogen and R_6 is selected from hydrogen, and substituted or unsubstituted alkyl, alkoxyalkyl, aminoalkyl, amidoalkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocyclo, and heteroarylalkyl.

65. A compound of Claim 58 wherein R_1 is taken together with R_2 to form a substituted or unsubstituted heterocycloalkyl or heteroaryl group.

66. A compound of Claim 58 wherein R_3 is loweralkoxy.

67. A compound of Claim 66 wherein R_3 is methoxy.

68. A compound of Claim 58 wherein R_4 is loweralkyl.

69. A compound of Claim 68 wherein R_4 is methyl.

70. A compound of claim 58 wherein R_1 is O, R_2 is NR_5R_6, R_5 is H, and R_6 is methyl.

71. A composition comprising an amount of a compound of claims 1, 16, 30, 44, or 58 effective to inhibit Raf activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

72. A composition of Claim 71 which further comprises at least one additional agent for the treatment of cancer.

73. A composition of Claim 72 in which the at least one additional agent for the treatment of cancer is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

74. A method of inhibiting Raf kinase activity in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 16, 30, 44 or 58 effective to inhibit Raf kinase activity in the human or animal subject.

75. A method for treating a cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 16, 30, 44 or 58 effective to inhibit Raf kinase activity in the human or animal subject.

76. A method of claim 75 which further comprises administering to the human or animal subject at least one additional agent for the treatment of cancer.

77. A method of claim 76 in which the at least one additional agent for the treatment of cancer is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

78. A method for treating a hormone dependent cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 16, 30, 44 or 58 effective to inhibit Raf kinase activity in the human or animal subject.

79. A method of claim 78 wherein the hormone dependent cancer is breast cancer or prostate cancer.

80. A method of claim 78 which further comprises administering to the human or animal subject at least one additional agent for the treatment of cancer.

81. A method of claim 80 in which the at least one additional agent for the treatment of cancer is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

82. A method for treating a hematological cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 16, 30, 44 or 58 effective to inhibit Raf kinase activity in the human or animal subject.

83. A method of claim 82 which further comprises administering to the human or animal subject at least one additional agent for the treatment of cancer.

84. A method of claim 83 in which the at least one additional agent for the treatment of cancer is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

85. A compound of claims 1, 16, 30, 44 or 58 for use in the treatment of cancer.

86. Use of a compound of claims 1, 16, 30, 44 or 58 in the manufacture of a medicament for the treatment of cancer.

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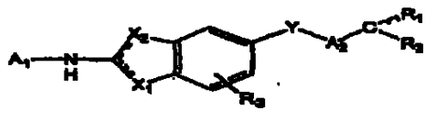
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(54) Título: BENZ-AZOLES SUSTITUIDOS Y SU APLICACIÓN COMO INHIBIDORES QUINAZA RAF



(I)

(57) Resumen: Nuevos compuestos benz-azola sustituidos de fórmula (I), composiciones y métodos de inhibición de actividad Raf quinases en sujetos humanos o animales son proveídos aca. Los nuevos compuestos de composición pueden ser usados solos o en conjunto con al menos un agente adicional para el tratamiento del desorden medicado Raf quinases, como el cáncer.

WO 03/082272 A1

BENZ-AZOLES SUSTITUIDOS Y SU APLICACIÓN COMO INHIBIDORES QUINAZA RAF

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con los nuevos compuestos sustituidos tipo benzazol y sales, ésteres o fármacos farmacéuticamente aceptables, con formulaciones de nuevos compuestos junto con portadores farmacéuticamente aceptables, y usos de los nuevos compuestos, ya sea solos o en combinación con al menos un agente terapéutico adicional, en la prevención o tratamiento del cáncer.

ANTECEDENTES DE LA INVENCIÓN

Las Quinazas Serina/Treonina RAF son componentes esenciales de la Quinaza Proteínica Ras/Mitogen-activada (MAPK) y señalan el módulo que controla un programa complejo transcripcional en respuesta a un estímulo celular externo. El código de genes Raf altamente conservado en las Quinazas Proteínicas específicas Serina/Treonina se sabe que va ligado a los oncogenes Ras. Son parte de una vía de transducción de señal que se cree consiste de un receptor Quinaza Tiroxina, p21 Ras, Quinaza Proteínica Raf, Quinazas MEK 1 (activador ERK o MAPK) y Quinazas ERK (MAPK), las cuales en ultima instancia son factores de trascripción fosforilato. De esta manera, las Quinazas Raf son activadas por el Ras

y el fosforilato y siendo activadas dos isoformas de Quinaza Proteínica Mitogen activada (llamadas Mek 1 y Mek 2), que son Quinazas Treonina/Tiroxina de especificidad dual. Ambas isoformas Mek activan las Quinazas Mitogen activadas 1 y 2 (MAPK, también llamadas Quinazas Regulada con Unión Extracelular 1 y 2 o Erk 1 y Erk 2). Los fosforilatos MAPKs son varios substratos incluidos los factores de la trascripción y los que posicionan su programa trascripcional. La participación de la Quinaza Raf en la vía Ras/MAPK consiste en influir y regular muchas funciones celulares tales como la proliferación, diferenciación, supervivencia, transformación oncogénica y apoptosis.

Tanto el papel esencial como la posición del Raf en muchas rutas señaladas han sido demostrados a partir de estudios, que involucran mutantes con acción deregularizada e inhibitoria dominante en células de mamíferos, así también como a partir de estudios que emplean técnicas bioquímicas y genéticas aplicadas a modelos de organismos. En muchos casos, la activación del Raf por receptores que estimulan la fosforilación celular de la Tiroxina es dependiente de la actividad del Ras, indicando que ésta actúa en contra del Raf. Luego, sobre la activación, el Raf-1 fosforila y activa el Mek 1, resultando en la propagación de la señal a factores derivados tales como MAPK (Quinaza Proteínica Mitogenactivada) (Crews et al. (1993) Célula 74:215). Los Raf de Quinaza Serina/Treonina son considerados como los primarios "efectores" Ras involucrados en la proliferación de células animales (Avrusch et el (1994) Tendencias Bioquímicas. Ciencia 19:279).

La Quinaza Raf tiene tres isoformas distintas, Raf 1 (c-Raf), A- Raf, y B- Raf, distinguidas por su capacidad de interactuar con el Ras, activar la ruta de la Quinaza MAPK, distribuir el tejido fino y en la localización sub-celular. (Marias et al., Bioquímica J. 351:289-

305,2000; Weber et al., Oncogén 19:169-176,,2000; Pritchard et al., Mol. Cel. Biol..15:6430-6442,1995). Las Quinazas Raf son activadas por el Ras y fosforilan por activadores isofórmicos de la Quinaza Proteínica Mitogen Activada (llamadas Mek 1 y Mek 2) que son Quinazas Treonina/Tiroxina de especificidad dual. Ambas isoformas Mek activan las Quinazas Mitogen activadas 1 y 2 (MAPK, también llamadas Quinaza Regulada Extracelular ligante 1 y 2 o Erk 1 y Erk 2). Los fosforilatos MAPKs son varios substratos incluidas las proteínas sistólicas y la familia de los factores de trascripción ETS. La participación de la Quinaza Raf en la ruta Ras/MAPK consiste en influir y regular muchas funciones celulares tales como la proliferación, diferenciación, supervivencia, progresión del ciclo celular y "apoptosis".

La mutación activada de uno de los genes Ras puede ser vista en ~20% de todos los tumores y la ruta Raf/MEK/ERK es activada en ~30% de todos los tumores. (Bos et al., Cáncer Res. 49:4682-4689,1989) (Hoshino et al., Oncogén 18:813-822,1999). Estudios recientes han mostrado que la mutación B Raf en la hiperplacia de la epidermis de la piel es una etapa crítica en la iniciación de la neoplasia melanocítica (Pollock et al., Nature Genetics 25:1-2,2002). Además, estudios más recientes han descubierto que la mutación en el dominio de la Quinaza del B-Raf ocurre en ~66% de los melanomas, 12 % en el carcinoma de colon y 14% en el cáncer de hígado (Davies et al., Nature 417:949-954,2002) (Yuen et al., Investigación sobre el Cáncer 62:6451-6455, 2002) (Brose et al., Investigación sobre el Cáncer 62: 6997-7000,2002).

Los inhibidores de la ruta Raf/MEK/ERK al nivel de las Quinazas Raf pueden ser potencialmente efectivos como agentes terapéuticos contra tumores con grandes dimensiones

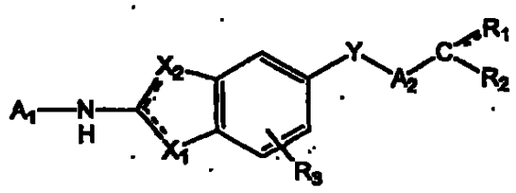
o Quinazas Tiroxina receptoras mutadas, Quinazas Tiroxina activadas intracelularmente, tumores con que se manifiestan de manera "aberrante" Grb2 (una proteina que sirve como adaptador y que permite la estimulación del Ras por el factor de intercambio Sos) así como los tumores que albergan mutaciones activadas del Raf mismo. Los ensayos clínicos iniciales con el inhibidor de la Quinaza Raf 1 que también inhibe la B- Raf han demostrado de manera prometedora ser agentes terapéuticos en el tratamiento del cáncer. (Crump, Diseño Farmacéutico Corriente 8:2243-2248,2002; Sebastien et. Al., Diseño Farmacéutico Corriente 8:2249-2253,2002).

La ruptura de la expresión Raf en las líneas celulares a través de la aplicación de la tecnología "antisense" (anti-sentido) RNA ha estado demostrando como se suprimen tanto la tumorgenicidad Ras y la Raf mediana. (Kolch et. Al., Naturaleza 349:416-428,1991; Monia et. Al., Medicina Naturista 2(6):668-675,1996).

Varios inhibidores Quinaza Raf han sido descritos como eficaces en la inhibición de la proliferación de células tumorales en ensayos *in vitro* o *in vivo* (ver, e, g., U.S. pat. Nos.6,391,636,6,358,932,6,037,136,5,717,100,6,458,813,6,204,467, y 6,268,391). Otras patentes y aplicaciones de patente sugieren el uso de inhibidores de la Quinaza Raf para el tratamiento de la leucemia. (ver, e, g., U.S. patente Nos. 6,268,391, y 6,204,467, y Aplicación de Patente publicada U.S. Nos 20020137774; 20020082192; 20010016194; y 20010006975), o para tratamiento del cáncer de seno (ver e.g., U.S. patente Nos 6,358,932,5,717,100,6,458,813,6,268,391, y 6,204,467 y Aplicación de Patente publicada U.S. No. 20010014679).

RESUMEN DE LA INVENCIÓN

Los nuevos compuestos de benz-azoles sustituidos y sales farmaceúticamente aceptables o ésteres que tienen una solubilidad imporntate de los principios activos están provistos de la Fórmula (I):



(I)

De donde, X_1 y X_2 son seleccionadas independientemente de: =N, -O O –S-, siempre que si X_1 es -NH_4 , -O-, -S-, entonces X_2 es =N, o si X_2 es –NH_4 -, -O- o – S-, entonces X_2 es =N y tanto X_1 y X_2 no son =N;

Y es O ó S.

A_1 es un alquil, cicloalquil, heterocicloalquil, aril, aril policíclico, aril alquil policíclico, heteroaril, biaril, heteroaril, heteroaril heteroaril, cicloalquilalquil, heterocicloalquil, arilalquil, heteroarilalquil, biarilalquil o heteroarilarilalquil sustituido o no sustituido;

A_2 es un heteroaril sustituido o no sustituido;

R_1 es un O ó H y R_2 es NR_5R_6 o hidroxil; o R_1 es tomado junto con R_2 para formar un heterocicloalquil sustituido o no sustituido o un grupo heteroaril; donde, la línea punteada representa un enlace sencillo o doble;

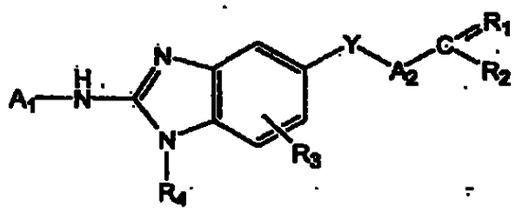
R_3 es un H, halógeno, alqui bajo, o alcoxi bajo (-bajo- peso molecular);

R_4 es un H, hidroxil, alquilamin, dialquilamin, o alquil;

R_5 y R_6 son seleccionados independientemente a partir de H, y un alquil, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, heteroarilalquil ; sustituido o no sustituido o R_5 y R_6 son tomados juntos para formar heterociclo o heteroaril sustituido o no sustituido;y

las sales farmaceúticamente aceptables o ésteres y pro fármacos correspondientes.

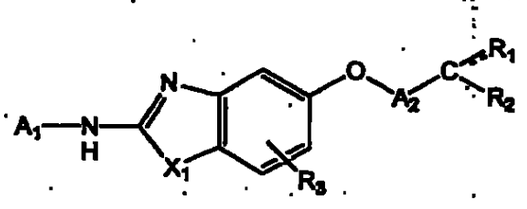
En otras versiones, nuevos compuestos de benz-azoles sustituidos están provistos por la Fórmula II:



(II)

donde Y, Ar_1,Ar_2, R_1,R_2, R_3 y R_4 están definidas como anteriormente; ;y las sales farmacéuticamente aceptables, ésteres, tautómeros y pro fármacos.

En otras versiones, nuevos compuestos de benz-azoles sustituidos están provistos por la Fórmula III:

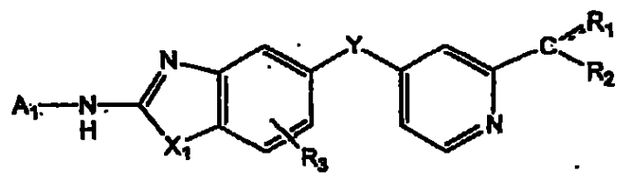


(III)

De donde X_1, Ar_1,Ar_2, R_1,R_2 y R_3 están definidas atrás; y

las sales farmaceúticamente aceptables, ésteres, tautómeros y pro fármacos correspondientes.

En otras versiones, nuevos compuestos de benz-azoles sustituidos están provistos por la Fórmula IV:

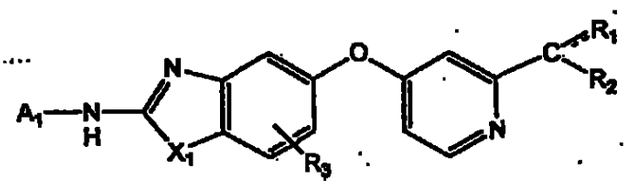


(IV)

De donde X_1, Y, Ar_1, R_1, R_2 y R_3 están definidas atrás; y

las sales farmaceúticamente aceptables, ésteres, tautómeros y pro fármacos correspondientes.

Aún en otras versiones, nuevos compuestos de benz-azoles sustituidos están provistos por la Fórmula V:



(V)

donde X_1, Ar_1, R_1, R_2 y R_3 están definidas atrás; ;y

las sales farmaceúticamente aceptables, ésteres, tautómeros y pro fármacos correspondientes.

En otros aspectos, la presente invención provee métodos para el tratamiento Raf relacionados con desórdenes en sujetos humanos y animales, los cuales requieren de un

tratamiento que le administra al sujeto una dosis del compuesto de Fórmulas (I), (II), (III), (IV) o (V).efectiva para reducir o prevenir el crecimiento del tumor en el sujeto, en combinación con, al menos, un agente adicional para el tratamiento del cáncer.

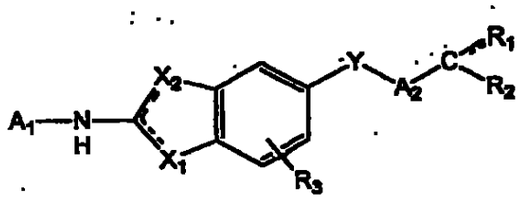
Además, la presente invención provee composiciones terapéuticas que abarcan al menos un compuesto de Fórmulas (I), (II), (III), (IV) o (V).en combinación con uno o más agentes adicionales para el tratamiento del cáncer, como son comúnmente empleados en la terapia del cáncer.

Los compuestos de la invención son utilizados en el tratamiento de cánceres, incluidos carcinomas (e.g., de los pulmones, páncreas, tiroides, vejiga, o colon), desórdenes del mieloide (e,g., leucemia del mieloide) y adenomas (e.g., adenoma del colon velloso).

Adicionalmente, la invención provee composiciones, métodos de uso, y métodos de manufactura como se describe en la descripción detallada de la invención.

DESCRIPCIÓN DETALLADA DE LA VERSIÓN PREFERIDA

En concordancia con uno de los aspectos de la presente invención los nuevos compuestos benz-azoles sustituidos y las sales farmacéuticamente aceptables, ésteres o pro fármacos están provistos por la Fórmula I :



(I)

donde, X_1 y X_2 son seleccionadas independientemente a partir de: =N, NR_4, -O- o –S-, provisto que si X_1 es $-NR_4$, -O-, -S-, entonces X_2 es =N, o si X_2 es $-NR_4$ -, -O- o – S-, entonces X_2 es =N y tanto X_1 y X_2 no son =N;

Y es O ó S.

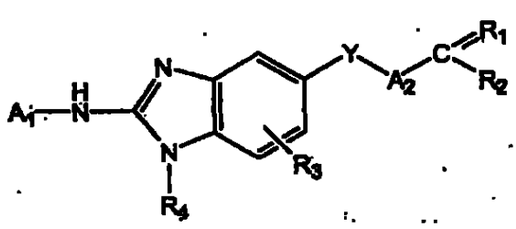
A_1 es un alquil, cicloalquil, heterocicloalquil, aril, aril policíclico, aril alquil policíclico, heteroaril, biaril, heteroaril, heteroaril heteroaril, cicloalquilalquil, heterocicloalquil, arilalquil, heteroarilalquil, biarilalquil o heteroarilarilalquil sustituido o no sustituido;

A_2 es un heteroaril sustituido o no sustituido; R_1 es un O ó H y R_2 es NR_5R_6 o hidroxil; o R_1 es tomado junto con R_2 para formar un heterocicloalquil sustituido o no sustituido o un grupo heteroaril; de donde, la línea rayada representa un enlace sencillo o doble; R_3 es un H, halógeno, alquil bajo, o alcoxi bajo (-bajo- peso molecular);

R_4 es un H, hidroxil, alquilamino, dialquilamino, o alquil;

R_5 y R_6 son independientemente seleccionadas a partir del H y de un alquil, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquilloxialquilheterociclo, y hateroarilalquil sustituido o no; R_5 y R_6 son tomados junto a las formas heterociclo o heteroaril sustituido o no sustituido; y las sales farmacéuticamente aceptables, ésteres y pro fármacos.

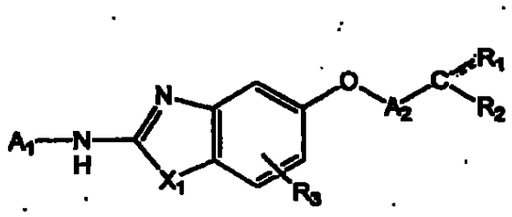
En otras versiones los nuevos compuestos benz-azoles sustituidos son provistos por la Fórmula (II):



(II)

donde , y, Y, Ar_1, Ar_2, R_1, R_2, R_3 y R_4 , son definidos como se indica anteriormente y las sales farmacéuticamente aceptables, ésteres y pro fármacos correspondientes.

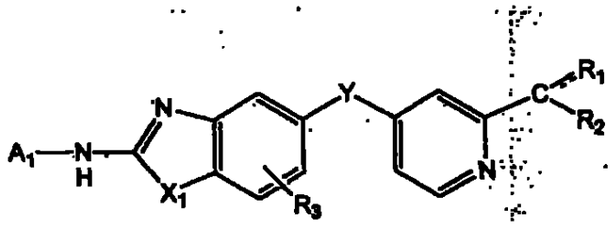
En otras versiones, nuevos compuestos benz-azoles sustituidos son provistos por la Fórmula (III):



(III)

donde X_1, Ar_1, Ar_2, R_1, R_2 y R_3 están definidos como se indica atrás, y las sales farmacéuticamente aceptables, ésteres, tautómeros y pro fármacos correspondientes.

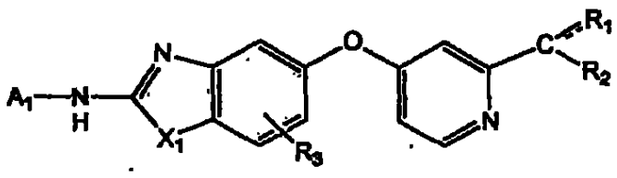
En otras versiones, nuevos compuestos benz-azoles sustituidos son provistos por la Fórmula (IV):



(IV)

donde X_1, Y, Ar, R_2, y R_3 están definidos como se indica atrás y las sales farmacéuticamente aceptables, ésteres tautómeros y pro fármacos correspondientes.

Aun más, en otras versiones, nuevos compuestos benz-azoles sustituidos son provistos por la Fórmula (V):



(V)

donde X_1, Ar_1, R_1, R_2 y R_3 están definidos como se indica atrás y las sales farmacéuticamente aceptables, ésteres, tautómeros y pro fármacos correspondientes.

En otro aspecto la presente invención provee métodos de tratamiento para seres humanos y animales que sufren un desorden relacionado con el RAF tal como el cáncer. Así, la presente invención provee métodos de tratamiento para seres humanos o animales que necesitan de un tratamiento que incluya la administración al sujeto de dosis terapéuticas efectivas de un compuesto de Fórmula I, II, III, IV o V indicada atrás, ya sea sola o mediante combinación con otros agentes anti-cancerígenos.

En otros aspectos, la presente invención provee métodos para el tratamiento relacionado con desórdenes Raf en sujetos humanos y animales que necesitan de tal tratamiento que incluya la administración a dicho sujeto de una cantidad efectiva de un compuesto de Fórmula (I), (II), (III), (IV) o (V), que reduzcan o prevengan el crecimiento tumoral en el paciente.

En otros aspectos, la presente invención provee métodos de tratamiento de los desórdenes relacionados con el Raf en sujetos humanos o animales que necesitan de tal tratamiento que incluya la administración a dichos sujetos de una dosis de un compuesto de Fórmula (I), (II), (III), (IV) o (V) efectiva para reducir o prevenir el crecimiento tumoral en el sujeto en combinación con, al menos, un agente adicional para el tratamiento del cáncer. Un número de anticancerígenos adecuados debe ser usado como combinaciones terapéuticas y que están contempladas en el uso de los métodos de la presente invención. Por supuesto, la presente invención contempla pero, no se limita a, la administración de números agentes anticancerígenos tales como: agentes que inducen la apoptosis, polinucleótidos (e.g., ribozomas); polipéptidos (e.g., enzimas); drogas; miméticos biológicos, alcaloides, agentes alquilantes, antibióticos antitumorales, antimetabolitos, hormonas, compuestos de platino,

anticuerpos conjugados monoclonales con drogas anticáncer, toxinas· y/o radionuclidos, modificadores biológicos de respuesta (ej. Interferones (ej.IFN-a,etc.), "interleukins"modificado [e.g., IL-2, etc], etc.); agentes de inmunoterapia adoptiva; factores de crecimiento hematopoiéticos; agentes que inducen la diferenciación de las células tumorales (e.g. todos los ácidos trans-retinoicos, etc.); reactivos de genoterapia; reactivos y nucleótidos de terapia anti- sentido; vacunas tumorales; inhibidores de angiogenesis y similares. Otros numerosos ejemplos de compuestos de quimioterapia y tratamientos anticáncer adecuados para co-administración con los compuestos comprendidos en las Fórmulas (I), (II), (III), (IV) o (V) son conocidos por los expertos en el tema.

En versiones preferidas, los agentes anticáncer pueden ser usados en combinaciones con compuestos de le presente invención que incluyen agentes que inducen o estimulan la apoptosis. Los agentes que inducen la apoptosis incluyen, pero no están limitados a, radiación (e.g.W); inhibidores Quinaza (e.g. inhibidor Quinaza del factor receptor del crecimiento epidérmico [E.G.F.R.], inhibidor Quinaza del factor receptor del crecimiento vascular [VGFR], inhibidor Quinaza del factor receptor del crecimiento fibroblástico [FGFR], inhibidor Quinaza I del factor receptor del crecimiento derivado de las plaquetas [PGFR] e inhibidores Quinaza Bcr-Abl tales como STI-571, Gleerev y Glivec]); moléculas antisentido; anticuerpos [e.g.,flutamida, bicalutamida, finasterida, aminoglutetamida, ketoconazol y cortisteroides]; inhibidores cicloxigenasa 2 (COX-2) (e.g., Celecoxib, meloxicam, N5-398 y drogas anti-inflamatorias no esteroidales [NSAIDs]; drogas de quimioterapia para el cáncer, (e.g., irinotecan (Camptosar), CPT-11, fluradabina (Fludara), dacarbazina (DTIC), dexamatexona, mitoxantrona, Mylotarg, VP-16, cisplatium, 5-FU, Doxrubicin, Taxotere o taxol); moléculas señaladoras celulares; ceramidas y citoquinas; y estaurosprinas y similares.

En otras aspectos, la presente invención provee composiciones farmacéuticas que incluyen al menos uno de los compuestos de las Fórmulas I, II, III, IV o V junto con un portador o vehículo farmacéuticamente aceptable y adecuado para administrarlo a sujetos humanos o animales, ya sea solo o en conjunto con otros agentes anticancerígenos.

En otros aspectos, la presente invención provee métodos de manufactura de los compuestos de Fórmulas (I), (II), (III), (IV) o (V) como se describe en este documento.

En otros aspectos, la presente invención provee compuestos los cuales son inhibidores de las enzimas Quinaza Raf, siendo la enzima un efecto secundario del p21ras; los inhibidores instantáneos son útiles en composiciones farmacéuticas para uso humano o veterinario donde la inhibición de la ruta de la Quinaza Raf es indicada, e.g., en el tratamiento de tumores o crecimiento celular canceroso mediado por la Quinaza Raf.

En particular, los compuestos son útiles en el tratamiento humano o animal, e.g., "murine" cáncer, puesto que la progresión de estos cánceres depende de la transducción en cascada de la señal proteínica del Ras y por lo tanto, es susceptible al tratamiento por la interrupción de la cascada inhibiendo la actividad de la Quinaza Raf. De acuerdo con esto, los compuestos de la invención son usados en el tratamiento de cánceres sólidos, tales como, por ejemplo, carcinomas, (e.g., de los pulmones, páncreas, tiroides, vejiga o colon, desórdenes del mieloide (e.g., leucemia del mieloide) o adenomas (e.g.., adenoma del colon velloso).

Los "inhibidores Raf" aquí usados se refieren a compuestos que exhiben un IC50 con respecto a la actividad de la Quinaza Raf no mayor a 100 milimicras y mas típicamente no mayor de 50 milimicras, medidas en el ensayo de filtración Raf/mek. Generalmente descritos más adelante. Las isoformas preferidas de la Quinaza Raf presentes en los compuestos de la presente invención demuestran que inhibirán incluso a las A-Raf, B-Raf y C-Raf (Raf-1). "IC50" es la concentración del inhibidor que reduce la actividad de una enzima (e.g., Quinaza

Raf) a la mitad del máximo nivel. Los compuestos representativos de la presente invención se ha comprobado que tiene actividad inhibitoria contra el Raf. Los compuestos de la presente invención exhiben un IC50 con respecto al Raf no mayor de 100 milimicras, aún más preferiblemente no mayor de 5 milimicras y todavía aún no mayor de 1 milimicras y lo más preferible es que no sobrepase los 200 μM, medidos en los ensayos de la Quinaza Raf descritos aquí.

Como se han usado aquí, los términos "benz-azoles" incluyen benzimidazoles, benzotiazoles y benzoxazoles.

La frase "alquil" se refiere a los grupos alquil que no contienen heteroátomos. Así que están incluidos grupos alquil de cadena lineal tales como metil, etil, propil, butil, pentil, hexil, heptil, octil, nonil, decil, undecil, dodecil, y similares. La frase tambien incluye los isómeros de cadena ramificada de los grupos alquil de cadena lineal, incluyendo pero sin limitarse a, los siguientes, a manera de ejemplos: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(C_2H_5)$, $-CH_2CH(C_2H_5)_2$, $-CH_2C(CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(C_2H_5)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(C_2H_5)$, $-(CH_2)_2CH(C_2H_5)$, $-(CH_2)_2C(CH_3)_3$, $-(CH_2)_2C(C_2H_5)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(C_2H_5)CH(CH_3)-CH(CH_3)(C_2H_5)$, y otros. La frase también incluye los grupos alquil cíllicos tales como ciclopropil, ciclobutil, ciclopentil, ciclohexil, cicloheptil, y ciclooctil y los anillos sustituidos con los grupos alquil de cadena lineal y ramificada descritos anteriormente. Así que la frase grupos alquil incluye grupos alquil primarios, secundarios y terciarios. Los grupos alquil preferidos incluyen cadenas lineales y ramificadas y grupos alquil cíclicos que contienen entre 1 a 12 átomos de carbono.

El término "-bajo--alquil" o "alquil menor" descrito aquí, incluye ambos grupos alquil con cadenas lineales o ramificadas que tienen de 1 a 6 átomos de carbono. Los grupos -bajo-alquil representativos incluyen , por ejemplo, metil, etil, propil, isopropil, n- butil, ter- butil, neopentil, trifluorometil, pentafluoroetil y similares. Los grupos -bajo- alquil pueden ser sustituidos con grupo halo, hidroxi, amino, nitro y/o ciano y similares. Otros -bajo-s alquil incluyen, por ejemplo, clorometil, triclorometil, cloroetil, hidroxietil, y similares. Otros -bajo-alquilos sustituidos incluyen, por ejemplo, aralalquil, aminoalquil, aminoaralalquil, carbonilaminoalquil, alquicarbonilaminoalquil, arilcarbonilaminoalquil, aralquilcarbonilamino alquil, aminoalcoxialquil y arilaminoalquil.

"Bajo- alcoxi" se usa acá para referirse a RO- en donde R es -bajo-alquil. Ejemplos representativos de grupos -bajo- alquil incluyen metoxi, etoxi, t-butoxi, trifluorometoxi y similares.

Como se usa acá, el término "halógeno" o "halo" se refiere a los grupos cloro, bromo, fluor e iodo. Haloalquil se refiere a un radical alquil sustituido con uno o más átomos de halógenos.

El término "halo--bajo--alquil" se refiere al radical -bajo- alquil sustituido con uno o más átomos halógenos.

El término "haloalcoxi" se refiere a un radical alcoxi sustituido con uno o más átomos halógenos. El término "halo--bajo--alcoxi" se refiere a un radical -bajo-alcoxi sustituido con uno o más átomos halógenos.

El término "amino" usado acá se refiere al grupo $-NH_2$. El término alquilamino se refiere según lo usado acá al grupo –NRR' donde R y R' son cada uno seleccionados independientemente de hidrógeno o de un -bajo-alquil. El término arilamino se refiere acá al grupo –NRR' donde R es un aril y R' en un hidrógeno, un -bajo-alquil o un aril. El término

aralquilamino se refiere acá al grupo – NRR' donde R es un -bajo-aralquil y R' es un hidrógeno, un -bajo-alquil, un aril o un -bajo-aril.

El término "alcoxialquil" se refiere al grupo $-alk_1-O-alk_2$ donde alk_1 es alquil o alquenilo y alk_2 es alquil o alquenilo. El término arilxialquil se refiere al grupo –alquil-O- aril. El término aralcoxialquil se refiere al grupo – alquilenil-o-aralquil, donde aralquil es un -bajo-alquil.

El término "alcoxialquilamino" se refiere acá al grupo –NR-alcoxialquil, donde R es típicamente hidrógeno, -bajo--aralquil o -bajo--alquil. El término amino--bajo--alcoxialquil se refiere acá a un aminoalcoxialquil en el cual el alcoxialquil es un -bajo--alcoxialquil.

El término "aminocarbonil" se refiere acá al grupo $-C(O)-NH_2$. amino carbonil sustituido se refiere acá al grupo –C(O)-NRR' donde R es un -bajo-alquil y R' es un hidrógeno o un -bajo-alquil. El término "arilaminocarbonil" se refiere acá al grupo –C(O)-NRR' donde R es un aril y R' es hidrógeno, -bajo-alquil o aril. El término "aralquilaminocarbonil" se refiere acá al grupo –C(O)-NRR' donde R es un -bajo-alquil y R' es un hidrógeno, -bajo-alquil o -bajo--aralquil.

"Aminosulfonil" se refiere acá al grupo $-S(O)_2-NH_2$. "Aminosulfonil sustituido" se refiere acá según lo adjunto al grupo $-S(O)_2-NRR'$ donde R es un -bajo-alquil y R' es un hidrógeno o -bajo-alquil. El término aralquilaminosulfonilaril se refiere acá al grupo –aril-$S(O)_2$-NH-aralquil donde el aralquil s un -bajo-alquil.

"Carbonil" se refiere al grupo divalente –C(O)-.

"Carboniloxi" se refiere generalmente al grupo –C(O)-O. Tales grupos incluyen ésteres, -C(O)-O-R, donde R es -bajo-alquil, cicloalquil, aril, o -bajo-aralquil. El término "Carboniloxicicloalquil" se refiere acá generalmente tanto a un "Carbonilcarbocicloalquil" y a un "Carboniloxiheterocicloalquil", i.e, donde R es un carboxicicloalquil o heterocicloalquil,

respectivamente. El término aril carboniloxi se refiere acá al grupo –C(O)-O-aril, donde el aril es un carbocicloaril o heterocicloaril mono o policíclico. El término "aralquilcarboniloxi" se refiere acá al grupo –C(O)-O-aralquil, donde el aralquil es un -bajo-aralquil.

El término sulfonil se refiere acá al grupo -SO_2-. "Alquilsulfonil" se refiere a un sulfonil sustituido de la estructura –SO_2R- donde R es alquil. Los grupos alquilsulfonil empleados en los compuestos de la presente invención son típicamente grupos -bajo-alquilsulfonil que tienen de 1 a 6 átomos de carbono en su estructura de espina dorsal. Así, los grupos alquilsulfonil típicos empleados en los compuestos de la presente invención incluyen, por ejemplo, metilsulfonil (i.e. donde R es metil), etilsulfonil (i.e. donde R es etil), propilsulfonil (i.e. donde R es propil) y similares. El término "arilsulfonil"se refiere aquí al grupo –SO_2-aralquil. El término "sulfonamido" se refiere acá al grupo -SO_2-NH_2.

Como se ha usado aquí, el término "carbonilamino" se refiere al grupo divalente –NH-C(O)- en el cual el átomo de hidrógeno de la amida nitrogenada del grupo carbonilamino puede ser reemplazada por un grupo -bajo-alquil, aril o -bajo-aralquil. Tales grupos incluyen compuestos tales como ésteres carbamatos (-NH-C(O)-O-R) y amidas .NH-C(O)-O-R donde R es un -bajo-alquil, cicloalquil aril o -bajo-aralquil de cadena lineal o ramificada. El término "-bajo-alquil carbonilamino" se refiere al alquil carbonilamino donde R es un -bajo-alquil que tiene 1 a 6 átomos de carbono en su estructura de espina dorsal. El término "arilcarbonilamino" se refiere al grupo –NH-C(O)-R donde R es un aril. De la misma manera, el término "aralquilcarbonilamino" se refiere al grupo carbonilamino donde R es un -bajo-aralquil. Como es usado aquí, el término "aminocarbonil" se refiere al grupo divalente –C(O)-NH en el cual el átomo de hidrógeno de la amida nitrogenada del grupo carbonilamino puede ser reemplazado por un grupo -bajo-alquil, aril o -bajo-aralquil, como se describió antes.

Como se usa aquí, el término "guanidin" o "guanidil" se refiere a derivados de la guanidin, H_2N-C(=NH)-NH_2. Tales derivados incluyen aquellos enlazados al átomo de nitrógeno que portan el enlace doble formal (la "2" posición de la guanidin, e.g., diaminometilamino, (H_2N)C=NH-) y aquellos átomos de nitrógeno que portan el enlace sencillo formal la "1" posición o "3" posiciones de la guanidin, e.g., H_2N-C(=NH)-NH-). Los átomos de hidrógeno de cualquier de los nitrógenos pueden ser reemplazados con un sustituto adecuado, tal como un -bajo-alquil, aril o -bajo-aralquil.

Como se ha usado aquí el término "amidino" se refiere a los derivados de R-C(=N)-NR (el radical viene siendo el nitrógeno "N^{1}") y R-(NR')C=N- (el radical viene siendo el nitrógeno "N^{2}"), donde R y R´ pueden ser hidrógeno, -bajoalquil, aril o -bajo--aralquil.

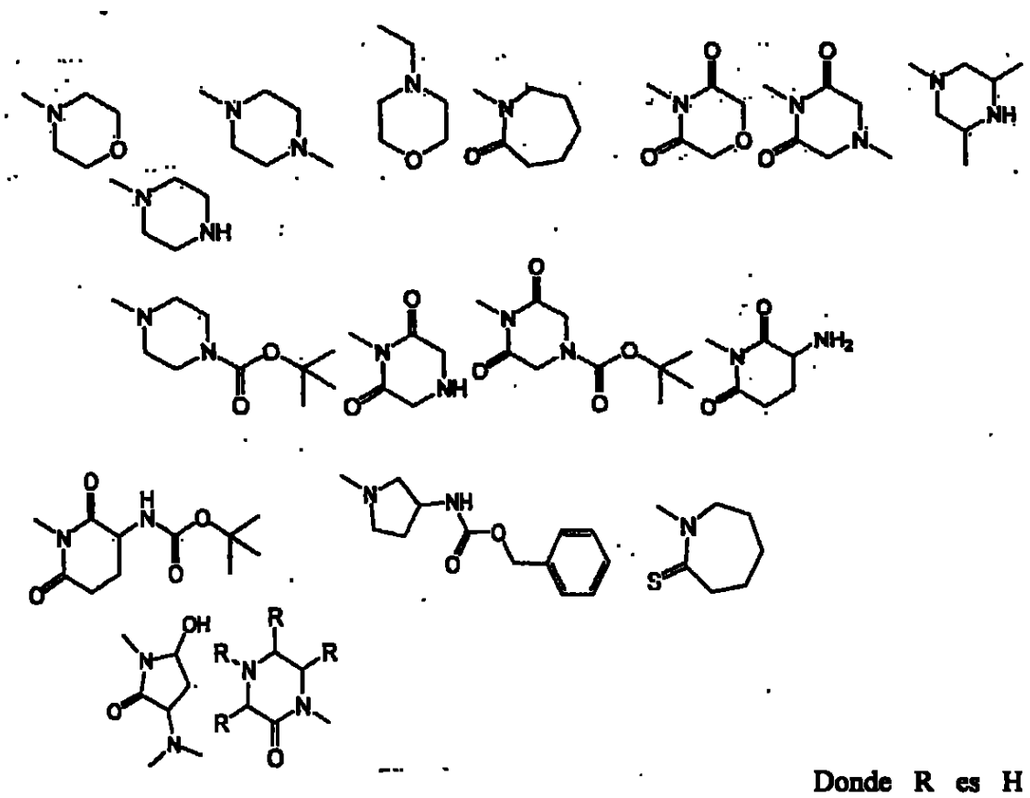
"Cicloalquil" se refiere al sustituto alquil mono o policíclico, heterocíclico o carbocíclico. Los típicos sustitutos del cicloalquil tienen de 3 a 8 átomos en sus estructuras vertebrales (i.e., anillo) en las cuales cada átomo de la estructura ó es un carbono o un heteroátomo. El término "heterocicloalquil" se refiere aquí a los sustitutos del cicloalquil que tienen de 1 a 5 y mas típicamente de 1 a 4 heteroátomos en la estructura del anillo. Los heteroátomos adecuados empleados en los compuestos de la presente invención son nitrógeno, oxigeno y azufre. Los heterocíclicos derivados representativos incluyen, por ejemplo, morfolino, piperazinil, piperadinil y similares. Los grupos carbocicloalquil son grupos cicloalquil en los cuales todos los átomos del anillo son carbonos. Cuando son usados en conexión con sustitutos cicloalquil, el término "policíclico" se refiere aquí a estructuras alquil cíclicas fusionadas y no fusionadas.

El término "heterocíclico sustituido" o "grupo heterocíclico" o heterociclo como se ha usado aquí, se refiere a cualquier anillo de 3 o 4 miembros que contienen un heteroátomo seleccionado de un nitrógeno, oxigeno y azufre o a un anillo con 5 o 6 miembros que

contienen de 1 a 3 heteroátomos seleccionados a partir del grupo consistente de N, O ó S; de donde el anillo de 5 miembros tiene 0-2 enlaces dobles y el anillo de 6 miembros tiene 0-3 enlaces dobles; de donde los heteroátomos de nitrógeno y azufre pueden ser opcionalmente cuaternarizados; e incluyen cualquier grupo bicíclico en el cual cualquiera de los anillos heterocíclicos mencionados es fusionado a un anillo bencénico o a otro anillo heterocíclico independiente de 5-6 miembros, definido arriba. El término "heterociclo" incluye también anillos parcial y totalmente saturados. Los heterociclos preferidos incluyen, por ejemplo diazapinil, pirril, pirrolinil, pirrolidinil, pirrazolil, pirazolinil, piperazinil, N-metil, piperazinil, azetidinil, N-metilazetidinil, pirimidinil, piridazinil, oxazolil, oxazolidinil, isoxazolil, isoazolidinil, morfolinil, tiazolil, tiazolidinil, isotiazolil, isotiazolidinil, indolil, quinolinil, isoquinolinil, bencimidazolil, benzotienil.

Los derivados heterocíclicos pueden ser no sustituidos, monosustituidos o di-sustituidos con varios sustitutos independientemente seleccionados a partir del hidroxi, halo, oxo(C=O), alquilimino (RN=, de donde R es un -bajo-alquil, o grupo -bajo-alcoxi), amino, alquilamino, dialquilamino, acilaminoalquil, alcoxi, tioalcoxi, polialcoxi, -bajo-alquil, cicloalquil o haloalquil.

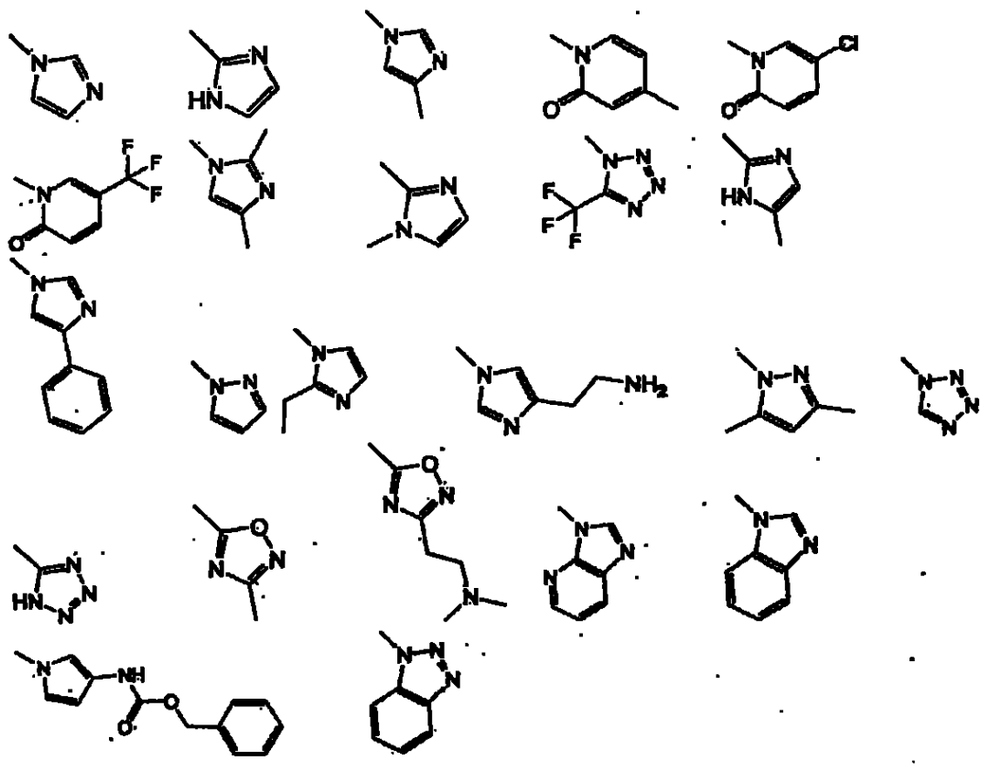
Los grupos heterocíclicos pueden ser añadidos a varias posiciones por aquellos expertos que aparentemente tengan habilidades en las artes de la química orgánica y medicinal en conjunción con lo tratado aquí.



Donde R es H o un sustituto heterocíclico, como se describió aquí.

Heterocíclicos representativos incluyen, por ejemplo, imidazol, piridil, piperazinil, azetidinil, tiazolil, furanil, triazolil, bencimidazolil, benzotiazolil, benzoxazolil, quinolinil, isoquinolinil, quinazolinil, quinoxalinil, ftalazinil, indolil, naftapiridinil, indazolil y quinolizinil.

"Aril" se refiere a grupos aromáticos sustituidos monocíclicos y policíclicos que tienen de 3 a 14 átomos de carbono o heteroátomos en su estructura vertebral, e incluyen tanto grupos aril carbocíclicos y heterocíclico. Los grupos aril carbocíclicos son aquellos en los cuales todos los átomos del anillo son carbonos. El término "heteroaril" se refiere aquí al grupo aril que tiene 1 a 4 heteroátomos como átomos de anillo que son carbonos. Cuando es usado en conexión con sustitutos aril, el término "aril policíclico" se refiere a estructuras cíclicas fusionadas o no, en las cuales al menos una estructura cíclica es aromática, tal como,



Heteroarilos representativos incluyen por ejemplo: imidazolil, piridil, piperazinil, azetinidil, tiazolil, triazolil benzimidazolil, benzitiazolil, y benzoxazolil.

El término biaril se refiere a un grupo sustituto para el cual tiene dos grupos baril. Los cuales no son condensados del 1 al otro como enlace. Ejemplo de compuestos de biaril incluyen, por ejemplo: fenilbenceno, difenildiazona, 4-metiltio-1-fenilbenceno, fenoxibenceno, (2fenilitinil)benceno, difenil, cetona, (4-fenilbuta-1,3-dinil)benceno, fenilbenzilamina, (fenilmetoxi) benceno, y similares. Grupos biaril sustituidos opcionalmente preferidos incluyen: 2(fenilamino) - N- [4-(2-feniletinil)-fenil]acetamida, 1,4-difenilbenceno, N-[4-(2.feniletinil)-fenil]-2-[benzilamino] acetamida, 2-amino-N-[4-(2-fenilitinil)fenil]propanomida, 2-amino-N-[4-(2fenilitenil)fenil] acetamida, 2-(ciclopropilamino)-N-[4-(2-feniletinil)fenil] acetamida, 2-(cilopropilamino)-N-4-(2-feniletinil)-fenil]acetamida, 2-(etilamino)N-04(2feniletinil)fenil]-acetamida, 2-[(2-

metipropil)amino]- N-[4-(2-feniletinil)fenil]acetamida, 5-fenil-2H-benzo[d]1,3 - dioxeleno, 2-cloro-1-metoxi-4-fenilbenzona,2-[(imidazolilmetil)amino]-N- [4-(2-feniletinil)-fenil]acetamida, 4-fenil-1-fenoxibenzona, N-(2-amioetil)- [4-(2-feniletinil)fenil]carboxamida, 2-{[4-metifenil)metil]amino}-N-[4-(2-feniletinil)fenil]acetamida, 4-fenil-1-(trifluorometil)benceno. 1-butil -4fenil-benceno, 2-(ciclohexilamino)-N- -[4-(2-feniletinil)fenil]acetamida, 2-(etilmetilamino) -N-[4-(2-feniletinil)fenil]acetamida, 2-(butilamino)-N-[4-(2-feniletinil)fenil]acetamida, N-[4-(2-feniletinil)fenil]-2-(4-piridilamino)acetamida, -N-[4-(2-feniletinil)fenil]-2-(quinuclidin-3-ilamino)acetamida, -N-[4-(2-feniletinil)fenil]pirrolidin-2-ilcarboxamida, 2- amino-3-metil-N--[4-(2-fenilitinil)fenil]-butanamida, 4(4-fenilbuta-1,3-dinil)fenilamina, 2-(d_imetilamino) -N- [4-(2-fenilbuta-1,3dinil)fenil]- acetamida, 2-(etilamino)-N -[4-(4-fenilbuta,-1,3-diinil)fenil]- acetamida, 4-etil-1-fenilbenzona, 1-[4-(2-feniletinilbuta)fenil]etano1-ona, N-(1-carbonil-2-hidroxipropil)-[4-(4-fenilbuta-1,3diinil)fenil]-carboxamida, N-[4-(2-feniletinil)fenil]propanomida, 4-metoxifenil fenil cetona, fenil- N- benzamida, (ter-butoxi)-N-[4-(2-feniletinilbuta)fenil] carboxamida, 2-(3-fenilfonoxi)àcido etanohidroxamico , 3-fenilfenil propanoato, 1-(4-etoxifenil)-4-metoxibenceno, y -[4-(2-fenilitinil)fenil]pirrol.

El término "hetereorilaril" se refiere un grupo biaril en uno de los grupos aril es un grupo heteroaril Ejemplo: heteroarilaril , incluyen, por ejemplo, 2-fenilpiridina, penilpirrol, 3-(2-feniletinil)piridina, fenilpirazol, 5-(2.feniletinil)-1,3-dihidropirimidina-2,4-diona, 4-fenil-1,2,3-tiadizol, 2-(2- feniletinil)pirazina, 2-feniltiofeno, fenilimidazol, 3-(2-piperazinilfenil) furano, 3-(2,4-diclorofenil)-4-metilpirrol, y similares. Grupos heteroaril sustituidos opcionalmente preferidos incluyen: 5-(2-feniletinil)pirimidina-2-ilamina, 1-metoxi-4-(2tienil)benceno, 1 metoxy-3-(2-tienil)benceno, 5-metil-2-fenil-piridina, 5-metil-3-

fenilisoxazol, 2-[3-(trifluorometil)fenil]furano, 3-fluor-5-(2-furil)-2-metoxi-1-prop-2-enilbenceno, (hidroximino)(5-fenil(2-tienil))-metano, 5-[(4-metilpiperazinil)metil]-2-feniltiofeno, 2-(4-etilfenil)tiofeno, 4-metiltio-1-(2-tienil)benceno, 2-(3-nitrofenil)tiofeno, (ter-butoxi)-N-[(5-fenil(3-piridil))-metil]carboxamida, hidroxi-N-[(5-fenil(3-piridil))metil]-amida, 2-(fenilmetiltio)piridina, y bencilimidazol.

El término "heteroarilheteroaril" se refiere a un grupo de biaril donde al grupo aril es un grupo .heteroaril Ejemplo de estos grupos incluyen 3-piridilimidazol, 2-imidazolipirazina, y similares. Grupos heteroarilheteroaril sustituidos preferidos incluyen: 2-(4-piperazinil-3-piridil)furano, dietil-(3-pirazin-2- y (4-piridil))amina, y dimetil{2-[2-(5-metilpirazina-2-il)etinil] (4-piridil)}amina.

"Opcionalmente sustituidos" o "sustituidos" se refiere al reemplazo del hidrógeno con un radical monovalente o bivalente. Algunos grupos de sustitución adecuados incluyen por ejemplo: hidroxil, nitro, amino, imino, ciano.halo, tio, sulfonil, tiomido, amidino, imidino. oxamilino, metoxamilino, guanidino, sulfanamido, carboxil, formil, -bajo-alquil, halo-bajo-alquil, -bajo-alquilamino, halo-bajo-alquilamino, -bajo-alcoxi, halo-bajo-alcoxi, -bajo-alcoxialquil, alquilcarboil, aminocarbonil, adilcarbonil, adolquilcarbonil, heteroalquilcarbonil, alquiltio,aminoalquil, cianoalquil, aril y similares.

El grupo de sustitución puede sustituirse a sí mismo. El grupo sustituido entre el grupo de sustitución puede ser, halo, nitro, amino, ciano, hidroxil, -bajo-alquil, -bajo-alcoxi, aminocarbonil- SR, tiamido, - SO_3H, SO_2R ó cicloaquil donde R es típicamente hidrógeno, hidroxil o -bajo-alquil.

Cuando los sustitutos sustituidos incluyen un grupo de cadena recta la sustitución

puede ocurrir entre esta cadena (e.g.,2-hidroxipropil,2-aminobutil y similares). Los sustitutos pueden ser de cadena recta, ramificada o conformaciones cíclicas de enlaces covalentes de carbono o heteroátomos.

Como se ha usado aquí, el término "grupo protector carboxi" se refiere a un grupo carbonil el cual ha sido esterificado con uno de los comúnmente usados grupos ésteres protectores de ácido carboxílico empleados para bloquear o proteger la función ácido carboxílico mientras reacciona involucrando otros sitios funcionales de los compuestos señalados. Además, un grupo protector carboxil puede ser añadido a un soporte sólido para lo cual el compuesto permanece conectado al soporte sólido, como el carboxilato hasta ser separado por métodos hidrolíticos que liberan el correspondiente ácido libre. Grupos protectores carboxil representativos incluyen,, por ejemplo ésteres -bajo-alquil amidas secundarias y similares.

Como se ha usado aquí, el término "sales farmacéuticamente aceptables" se refiere a ácido no tóxicos o sales alcalinotérreas metálicas de los compuestos de la Fórmula I.. Estas sales pueden ser preparadas "*in situ*" durante el aislamiento final y purificación de los compuestos de la Fórmula I, o por reacción separada de las funciones básica o ácida con un adecuado ácido o base orgánica o inorgánica, respectivamente. Dichas sales incluyen, sin limitarse a las siguientes: acetatos adipatos, alginatos, citratos, aspartatos, benzoatos, bencensulfonatos, bisulfatos, butiratos, canforatos, canforsulfanatos, digulconato, ciclopentanopropionatos, dodecilsulfatos, etanosulfanatos, glucoheptanoatos, glicerofosfatos, hemisulfatos, heptanoatos, hexanoatos, fumaratos, hidrocloruros, hidrobromuros, hidroioduros, 2- hidroxietanosulfonatos, lactatos, maleatos, metanosulfonatos, nicotinatos, 2-naftalensulfonatos, oxalatos, pamoatos, pectinatos, persulfatos, 3- fenilpropionatos, picratos, piralatos, propionatos, succinatos, sulfatos, tartratos, tiocianatos, p-toluenosulfonatos y

undecanoatos. También los grupos que contienen nitrógeno básico pueden ser cuaternarizados con agentes tales como haluros -bajo alquil, metil, etil, propil, cloruro de butilo, bromuros y ioduros; sulfatos dialquil como dimetil, dietil, dibutil y sulfatos de diamilo, haluros de cadena larga como decil, lauril, miristil y cloruros, bromuros y ioduros de estearil, haluros de aralquil (bromuros de bencil y fenetil) y otros. Agua, aceite soluble o productos dispersantes son, en consecuencia, obtenidos.

Ejemplos de ácidos que pueden ser empleados para formar sales de adición farmacéuticamente aceptables, incluyen ácidos inorgánicos como clorhídrico, sulfúrico, fosfórico y ácidos orgánicos como oxálico, maléico, metanosulfónico, succínico y cítrico. Sales básicas de adición pueden ser preparadas *in situ* durante el aislamiento final y purificación de los compuestos de la Fórmula I o separadamente por reacción de derivados de un ácido carboxílico de una base adecuada como el hidróxido, carbonato o bicarbonato de un catión metálico farmacéuticamente aceptable o con amoniaco, o una amina primaria, secundaria o terciaria. Las sales farmacéuticamente aceptables incluyen, sin limitarse a, cationes basados en metales alcalinotérreos y álcalis, tales como Na, Li, K, Ca, Mg, Sales de aluminio y similares, así como amonio atóxico o cuaternario y cationes amina, incluidos sin limitarse a, amonio tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, etilamina y similares. Otras aminas utilizadas para la formación de sales de adición básicas incluyen dietilamina, etilendiamina, etanolamina, dietanolamina, piperazina y similares.

Como se ha usado aquí el término "ésteres farmacéuticamente aceptables" se refiere a ésteres que se hidrolizan *in vivo* e incluyen aquellos que se rompen rápidamente en el cuerpo humano para dejar el compuesto padre o sal de este. Grupos de ésteres adecuados son aquellos derivados de ácidos carboxílicos alifáticos farmacéuticamente aceptables, particularmente

ácidos alcanóicos, alquenóico, cicloalcanóicos, alcanodioicos, en lo cuales cada derivado alquil o alquenil ventajosamente, no tiene más de 6 átomos de carbono. Por ejemplo, formiatos, acetatos, propinatos, butiratos, acrilatos y etilsuccinatos.

El término "pro fármacos farmacéuticamente aceptables" como se ha usado aquí, se refiere a aquellos pro fármacos de los compuestos de la presente invención. Los cuales están dentro del alcance del juicio profesional médico que aprueba su uso adecuado en el contacto con los tejidos humanos y animales sin excesiva toxicidad, irritación, respuesta alérgica y similares. Una discusión completa aparece en T. Higuchi y V. Stella, Pro Fármacos como Sistemas de Entrega Original, Vol. 14 de la serie de simposios A.C.S. y en Edward B. Roche ed., Portadores Bioreversibles en el Diseño de Fármacos, Asociación Farmacéutica Americana y Prensa Pergamon, 1987, los cuales se incluyen aquí en las referencias.

El término "cáncer" se refiere a enfermedades cancerígenas que pueden ser beneficiosamente tratadas por la inhibición de la Quinaza Raf incluidos, por ejemplo, cánceres sólidos tales como carcionomas (e.g., de los pulmones, páncreas, tiroides, vejiga o colón, desórdenes del mieloide (e.g.,leucemia del mieloide) y adenomas (e.g., adenoma del colón velloso).

En las versiones ilustrativas de la invención, Ar_1 puede ser, por ejemplo, fenil el cual puede ser sustituido por uno o más sustitutos seleccionados del grupo consistentes de hidroxil, nitro, ciano, halo y amino sustituido o no sustituido, imino, tio, sulfonil, tioamido, amidino, idino, oxo, oxaminido, metoxaminido, imidino, guanidino, sulfanomido, carboxil, formil, -bajo-alquil, halo-bajo-alquil, -bajo-alquilamino, halo-bajo--alquilamino, -bajo-alcoxi, -bajo-alcoxiaquil, alquilcarbonil, aminocarbonil, -bajo-alquilaminocarbonil, heterocicloalquil, -bajo-

alquil,aminocarbonil, carboxil -bajo-alquil, aminiocarbonil, arilcarbonil, aralquilcarbonil, heteroarilcarbonil, heteroarilcarbonil, heteroalquilcarbonil, alquitio, cianoalquil, aril y similares. En otras versiones ilustrativas de la invención, Ar_2 puede ser por ejemplo: piridil, el cual puede ser sustituido por uno o más sustitutos seleccionados a partir del grupo consistente de hidroxil, nitro, ciano, halo, y el aminosustituido o no sustituido, imino, tio, sulfonil, tioamido, amidino, imidiono, oxo, oxamidino, metoxamidino, guanidino, sulfonamido, carboxil, formil, -bajo-alquil, halo-bajo-alquil, -bajo-alquilamino, halo-bajo-alquilamino, -bajo-alcoxi, halo-bajo-alcoxi, -bajo-alcoxialquil, alquilcarbonil, aminocarbonil, -bajo-alquilaminocarbonil, heterocicloalquil, -bajo-alquilaminocarbonil, carboxil, -bajo-alquilaminocarbonil, arilcarbonil, aralquilcarbonil, heteroarilcarbonil, heteroalquilcarbonil, alquiltio, aminoalquil, cianoalquil, aril y similares.

En otras versiones ilustrativas de la invención, Ar_1 puede ser, por ejemplo, fenil el cual puede ser sustituido por uno o más sustitutos seleccionados del grupo consistentes de hidroxil, nitro, ciano, halo y amino sustituido o no sustituido, imino, tio, sulfonil, tioamido, amidino, idino, oxo, oxaminido, metoxaminido, imidino, guanidino, sulfanomido, carboxil, formil, -bajo-alquil, halo-bajo-alquil, -bajo-alquilamino, halo-bajo-alquilamino, -bajo-alcoxi, -bajo-alcoxiaquil, alquilcarbonil, aminocarbonil, -bajo-alquilaminocarbonil, heterocicloalquil, -bajo-alquil,aminocarbonil, carboxil -bajo-alquil, aminiocarbonil, arilcarbonil, aralquilcarbonil, heteroarilcarbonil, heteroarilcarbonil, heteroalquilcarbonil, alquitio, cianoalquil, aril y similares. En otras versiones ilustrativas de la invención, Ar 2 puede ser por ejemplo: piridil, el cual puede ser sustituido por uno o más sustitutos seleccionados a partir del grupo consistente de hidroxil, nitro, ciano, halo, y el aminosustituido o no sustituido, imino, tio, sulfonil, tioamido, amidino, imidiono, oxo, oxamidino, metoxamidino, guanidino,

sulfonamido, carboxil, formil, -bajo-alquil, halo-bajo-alquil, -bajo-alquilamino, halo-bajo-alquilamino, -bajo-alcoxi, halo-bajo-alcoxi, -bajo-alcoxialquil, alquilcarbonil, aminocarbonil, -bajo-alquilaminocarbonil, heterocicloalquil, -bajo-alquilaminocarbonil, carboxil, -bajo-alquilaminocarbonil, arilcarbonil, aralquilcarbonil, heteroarilcarbonil, heteroalquilcarbonil, alquiltio, aminoalquil, cianoalquil, aril y similares.

En versiones representativas de la invención, los compuestos de esta incluyen, por ejemplo: 4-{(2-{(4-cloro-3-(trifluorometil)fenil}amino}-1H-bencimidazol-6-il)oxi}-N-metilpiridina-2-carboxamida, 4-({2-{(3-clorofenil)amino}-1H-benzcimidazol-6-il}oxi)-N-metilpiridina-2-carboxamida, 4-({2-{4-bromofenil)amino}-1H-bencimidazol-6-il}oxi)-N-metilpiridina-2-carboxamida, 4-({2-{(3-cloro-4-fluorofenil)amino}-1H-bencimidazol-6-il}oxi)-N- metilpiridina-2- carboxamida, N-metill -4-{(2-(fenilamino)-1H-bencimidazol-6-il)oxi}piridina-2- carboxamida, 4-{(2-{(4-bromo-2-(trifluorometil)fenil}amino} -1H-bencimidazol-6-il)oxi}-N- metilpiridine-2-carboxamida, N-metil-4-({2-{(2-metilpropil)amino}-1H-bencimidazol-6-il}oxi)piridina-2-carboxamida, 4-{(2-{(4-(dimetilamino)nafthaleno-1-il}-amino}-1H-bencimidazol-6-il)oxi}-N- metilpiridina-2-carboxamida, N-metil-4-({2-{(4-nitrofenil)amino}-1H-bencimidazol-6-il}oxi) piridina-2-carboxamida, N-metil-4-({2-{(fenilcarbonil)amino}-1H-bencimidazol-6-il}oxi)piridina-2-carboxamida, N-metil-4-({fenilmetil)amino}-1H-bencimidazol-6-il}oxi)piridina-2-carboxamida, metil 4-{(6-({2-{(metilamino)carbonil}piridina-4-il}oxi)-1H-bencimidazol-2-il}amino}benzoato, 4-({2-{(4-clorofenil)amino}-1H-bencimidazol-6-il}oxi)-N- metilpiridina-2-carboxamida, 4-{(2-{(2-(etiloxi)fenil}amino}-1H-bencimidazol-6-il)oxi}-N- metilpiridina-2-carboxamida, N-metil-4-({2-{(2-morfolina-4-il-etil)-amino}-1H-bencimidazol-6-il}oxi)piridina-2-carboxamida, 4-({2-{(4-iodofenil)-amino}-1H-bencimidazol-6-il}oxi)-N-metilpiridina-2-carboxamida, N-metil-4-{(2-{(4-(trifluorometil)feni}amino}-1H-

benzcimidazol-6-il)oxi) -N- metilpiridina-2-carboxamida, 4-{(2-{(4-bromo-2-(trifluorometil)fenfl)amino}-1H-bencimidazol-6-il)oxi}-N- metilpiridina-2- carboxamida, N-metil-4-({2-{(2-{(2-metilpropil)amino}-1H bencimidazol-6-il)oxi}-N-metilpiridina-2-carboxamida, N-metil-4-({2-({(2-morfolina-4-il-etil)amino}-1H-bencimidazol-6-il}oxi)piridina-2-carboxamida, 4_-({2-({4-iodofenil)-amino}-1H-bencimidazol-6-il}oxi}-N-metilpiridina-2- carboxamida, N-metil-4-{(2-{(4-(trifluorometil)fenil}amino}-1Hbenzimidazol-6-yl)oxi}piridina-2-carboxamida, 4-({2-{(furano-2-il-metil)amino}-1H-bencimidazol-6-il}oxi)-N- metilpiridina-2-carboxamida, 4-({2-{(4-bromo-3-metilfenil)amino}-1H-bencimidazol-6-il}oxi}-N- metillpiridina-2-carboxamida, 4-({2-{(4-acetyphenyl)amino}-1H-bencimidazol-6-il}oxi}-N- metilpiridina -2-carboxamida, N-metil-4-({2,4,6-trimetilfenil)amino}-1H-bencimidazol-6-il}oxi}piridina-2-carboxamida, 4-{(2-{(4-(1,1-dimetiletil)fenil}amino}-1H-bencimidazol-6-il)oxi}-N- metilpiridina-2-carboxamida, 4-({2-{(2-bromofenil)amino}-1H-bencimidazol-6-il}oxi)-N- metilpiridina-2- carboxamida, 4-({2-({3-bromofenil)amino}-1H.-bencimidazol-6-il}oxi)-N- metilpiridina-2-carboxamida, 4-({2-{(2-clorofenil)amino}-1H-bencimidazol-6-il}oxi)-N- metilpiridina-2-carboxamida, metil 3-{(6-({2-{(metilamino)carbonil}piridina-4-il}oxi)-1H-bencimidazol-2-il}amino} tiofeno-2-carboxylato, 4-({4-bromofenil)amino}-1H-bencimidazol-6-il}oxi)-N- {(3R,5R)-5-{(metil)metil}pirrolidina-3-il}piridina-2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-metil-1H-bencimidazol-5-il}oxi)-N- metilpiridina-2-carboxamida, 4-{(2-{(4-cloro-3-(trifluorometil)fenil}amino}-1- metil-1H-bencimidazol-5-il)oxi}-N- metilpiridina-2-carboxamida, N-metil-4-{(1-metil-2-{(4-trifluorometil)fenil}amino}-1H-bencimidazol-5-il}oxi)piridina-2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-metil-1H-bencimidazol-5-il}oxi)-N- etilpiridina-2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-metil-1H-bencimidazol-5-il)oxi}-N, N-dimetilpiridina-2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-

metil-1H-bencimidazol-5-il}oxi)-N-(2,2,2-trifluoroetil)piridina-2-carboxamida, N-(4-bromofenil)-1-metil-5-{(2-pirrolidina-1-il-carbonil)piridina-4-il)oxi}-1H-bencimidazol-2-amina, etil (3R)-3-(metiloxi)-4-({(4-{2-{(4-(trifluorometil)fenil}amino}-1H-bencimidazol-5-il}oxi)piridina-2-il)carbonil_}amino)piperidina-1-carboxilato, 4-({2-{(4-bromofenil)amino}-1-metil-1H-bencimidazol-5-il)oxi}-N- {2-(dimetilamino)etil}piridina -2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-metil-1H-bencimidazol-5-il}oxi)-N- (tetrahidrofurano-2-il-metil)piridina-2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-metil-1H-bencimidazol-5-il}oxi)-N- (2-morfolina-4-iletil)piridina-2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-metill-1H-bencimidazol-5-il}oxi)-N-(piperidina-4-ilmetil)piridina 2-carboxamida, 5-({2-{(3-aminopirrolidina-1-il)carbonil}piridina-4-il)oxi}-N- (4-bromofenil)-1-metil-1H-bencimidazol-2-amina, 4-({4-bromofenil)amino}-1-metil-1H-benzimidazol-5-il)oxi}-N- {1-difenilmetil)azetidina-3-il}piridina-2- carboxamida, 4-({2-{(4-bromofenil)aminol}-1-metil-1H-bencimidazol-5-il}oxi)-N- piperidina-3-ilpiridina-2-carboxamida, 4-({2-{(4-bromofenil)amino}-1-metil-1H-bencimidazol-5-il}oxi)-N- (1,3-tiazol-2-il)piridina-2-carboxamida , 4-({2-{(4-bromofenil)amino}-1-metil-1H- bencimidazol-5-il}oxi)-N- {(1-etilpirrolidin-2-il)-metil}piridian -2-carboxamida, (4-{2-{(4-bromofenil)amino}benzotiazol-5-il)oxi}(2-piridil)}-N-metil carboxamida, (4-{2-({4-bromofenil)amino}benzoxazol-5-il)oxi}-(2-piridil))-N-metilcarboxamida, y otros compuestos representativos establecidos en el 4° de los ejemplos.

En otros aspectos, la presente invención relaciona los procesos para preparar los compuestos de la Fórmulas I, II, III, IV y V, y para sintetizar los intermedios usados en tales procesos.

Los compuestos de la invención abarcan átomos de carbono asimétricamente sustituidos. Los cuales pueden resultar en mezcla de estero-isómeros en un átomo de carbono

particular asimétricamente sustituido o en un estero-isómero sencillo. Lo cual resulta, en mezclas racémicas, mezclas de diasterómeros, así como de diasterómeros sencillos. En los compuestos de la invención que aquí se incluyen los términos de la configuración "S"y "R", aquí usados, están definidos por la IUPAC 1974 Recomendaciones para la Sección Estereo Química Fundamental –Química Aplicada para 45:B-30(1976). Los términos Alfa y Beta y B son empleados para posiciones del anillo en los compuestos cíclicos. El lado alfa de la referencia plana es aquel en el cual el sustituto preferido tiende a situarse en la menor posición; aquellos sustitutos que tienden a situarse en el lado opuesto de la referencia plana se les asigna la clase beta.

Debera notarse que este uso difiere a partir de los estero compuestos cíclicos en los cuales alfa significa "debajo del plano" y denota una configuración absoluta.

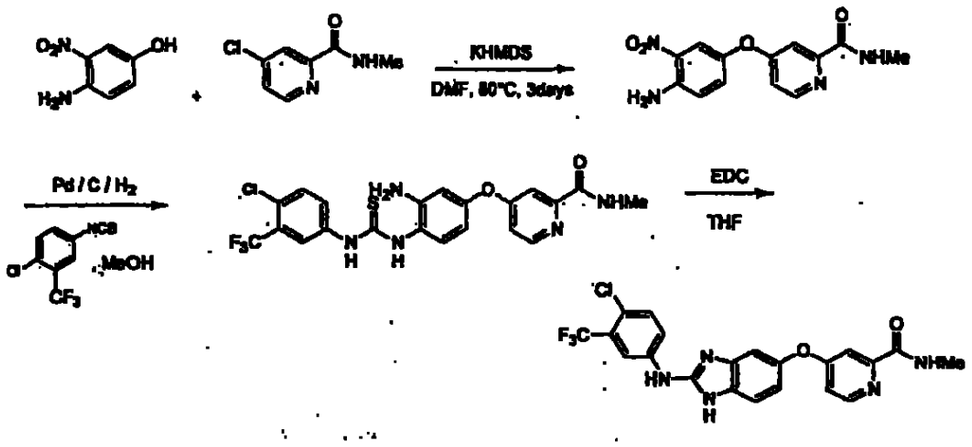
Los términos de las configuración alfa y beta usados aquí, están definidos por el Chemical Abstracts Index Guide- Apéndice IV (1987), parágRafo 203.

La presente invención también relaciona los procesos para la preparación de los componentes citados aquí y los intermedios utilizados en dichos procesos, como se describe en detalle más adelante-.

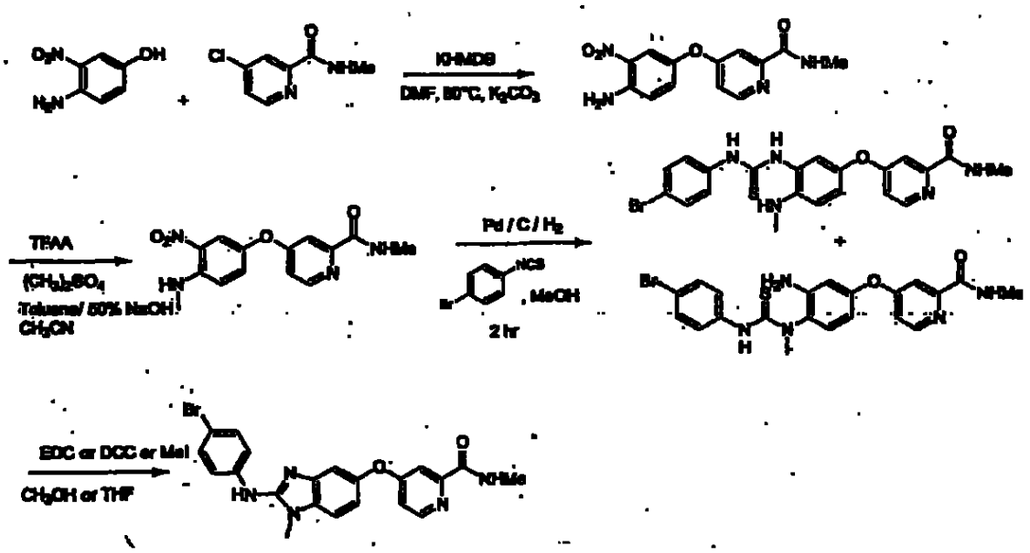
Métodos sintéticos

Los compuestos de la invención contienen un núcleo de bencimidazol que puede ser preparado usando un número de métodos familiares a alguien hábil en el arte. En un método, diaminas funcionales adecuadamente pueden ser acopladas con varios tioisocianatos para formar el intermedio tioúrea.

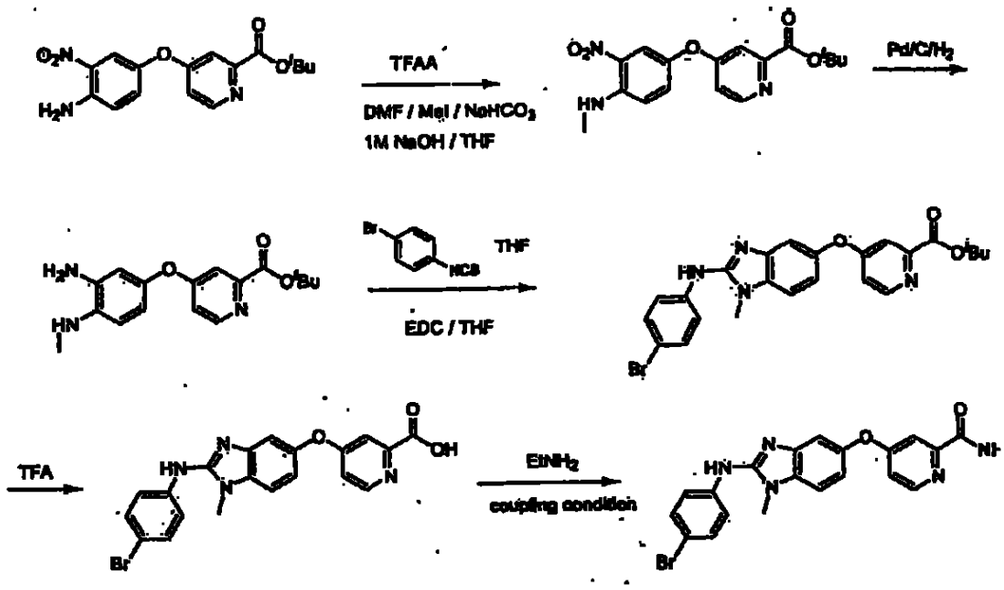
La ciclización para formar el derivado bencimidazol puede ser afectada -bajo- condiciones conocidas tales como el tratamiento de unas carbodiimidas o haluros de alquil como se muestra en los siguientes esquemas.



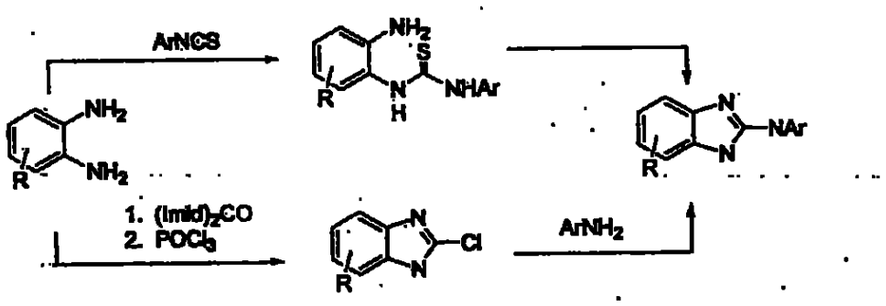
ESQUEMA



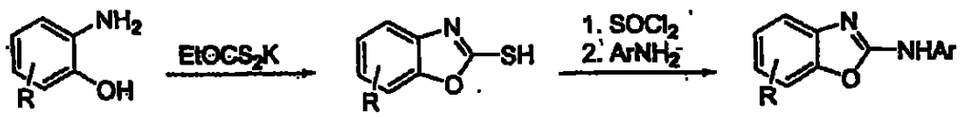
ESQUEMA



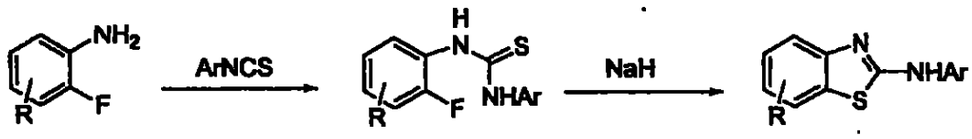
Alternativamente, las diaminas pueden reaccionar secuencialmente con carbonil diimidazol y cloruro de fósforilo seguido por acoplamiento con la amina apropiada.



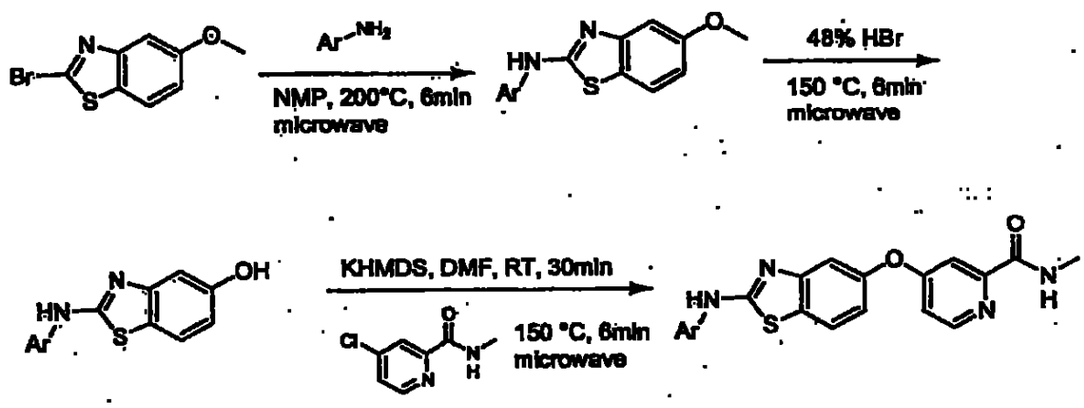
Los compuestos que contiene la estructura oxaxol pueden similarmente ser preparados de acuerdo con los métodos mostrados arriba o de acuerdo con otros procedimientos generales conocidos. Aviv et al.)J.Med. Chem.1988, 31:1719) describe un procedimiento para ensamblar núcleos de oxaxol en donde una hidroxianilina es tratada con xantato de tipo etilpotasio. La benzoxazol sulfuril resultante puede entonces ser clorinada y acoplada con una amina.



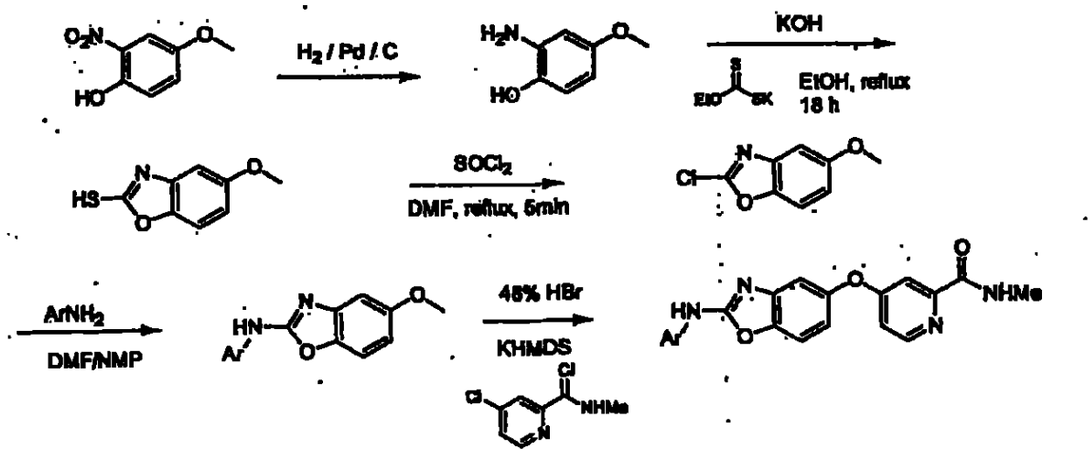
Los compuestos que contienen un núcleo de benzotiaxol pueden también ser preparados de acuerdo con los métodos conocidos. Un orto-halotioisocianato puede reaccionar con una amina para formar tioúrea. La reducción con NaH entonces permite la formación del anillo de tiazol.



Los benzotiazoles pueden generalmente ser sustituidos en concordancia con la presente invención, como a través de la siguiente ruta sintética:



Los benzoxazoles pueden generalmente ser sintetizados a través de la siguiente ruta:



Los compuestos de la invención son útiles *in vitro* o *in vivo* en la inhibición del crecimiento de las células cancerosas. Estos pueden ser usados solos o en composiciones. con un portador farmacéuticamente aceptable o excipiente. Dichos portadores incluyen, por ejemplo, agentes de procesamiento y modificadores de entrega de fármacos intensificadores, tales como, por ejemplo, fosfato cálcico, estearato de magnesio, talco monosacáridos, disacáridos, almidón, gelatina, celulosa, metilcelulosa, carboximetil celulosa, sodio, dextrosa y hidroxipropil, B- ciclodextrina, polivinilpilorridona, ceras de bajo punto de fusión, resinas de intercambio iónico, y similares, así como las combinaciones de dos más de estos.

Otros excipientes farmacéuticamente aceptables adecuados son descritos en"Remington's Pharmaceutical Sciencies", Mack Pub. Co, N.J(1991), incorporada aquí como referencia.

Cantidades efectivas de los compuestos de la invención generalmente incluyen cualquier cantidad suficiente detectable que inhiba la actividad Raf para cualquiera de los ensayos descritos aquí. Otros ensayos de la actividad de la Quinaza Raf pueden ser reconocidos por aquellos expertos en el arte o por detección de la inhibición o mitigación de los síntomas del cáncer.

La cantidad del ingrediente activo que puede ser combinado con los materiales portadores para producir una forma de dosis sencilla variará dependiendo del paciente tratado y del modo particular de administración. Será entendido, sin embargo, que el nivel de dosis específico para cualquier paciente particular dependerá de una variedad de factores que incluyen la actividad y el compuesto específico empleado, la edad, peso corporal, salud general, sexo, dieta, tiempo de administración, ruta de administración, tasa de excreción, combinación del fármaco y la severidad de la enfermedad particular sometida al tratamiento. La cantidad efectiva terapéuticamente para una situación dada puede ser rápidamente determinada por una rutina de experimentación, habilidad y juicio profesional del clínico ordinario.

Para propósitos de la presente invención, una dosis efectiva terapéuticamente generalmente será una administrada diariamente de manera total a un paciente en dosis sencillas o divididas que pueden ser en cantidades, por ejemplo a partir de 0.001 a 1000 mg/Kg del peso corporal diariamente. Las unidades de los compuestos de la dosificación pueden contener cantidades en submúltiplo de ellas de tal forma que completen la dosis diaria.

Los compuestos de la presente invención pueden ser administrados oralmente, parenteralmente, sublingualmente, por aerosolización o inhalación atomizada, rectalmente o típicamente en unidades dosificadas de formulación que contienen portadores convencionales farmacéuticamente aceptables atóxicos, coadyuvantes y vehículos deseados. La administración tópica puede involucrar el uso de la administración transdérmica tales como parches transdérmicos o dispositivos dérmicos o dispositivos de ionofóresis. El término parenteral como se ha usado aquí incluye inyecciones subcutáneas, intravenosas, intramusculares,

instraternales o técnicas de infusión.

Preparaciones inyectables, por ejemplo, suspensiones acuosas estériles u oleaginosas, pueden ser formuladas de acuerdo con la experiencia utilizando agentes adecuados dispersantes, humectantes o de suspensión. También, pueden ser una solución o suspensión en un diluyente aceptable parenteralmente atóxico, por ejemplo, una solución en 1,3-propanodiol. Entre los vehículos y solventes aceptables que pueden ser empleados son agua, solución de Ringer y solución de cloruro de sodio isotónico, además, aceites fijos estériles son convencionalmente empleados como un solvente o medio de suspensión para este propósito. Cualquier aceite suave fijo puede ser empleado, con los mono o di-glicéridos sintéticos. También. ácidos grasos, como el ácido oleico encuentran uso en dichas preparaciones.

Los supositorios para administración rectal del fármaco pueden ser preparados por mezcla de este con un excipiente no irritante adecuado como la mantequilla de cacao y el polietilen glicol, los cuales son sólidos a temperaturas ordinarias pero líquidos a la temperatura rectal y por lo tanto se fundirán en el recto y liberarán el fármaco.

Algunas formas de dosificación sólida para administración oral incluyen cápsulas, tabletas, píldoras, polvos y gránulos. En tales casos, el compuesto activo puede ser administrado con al menos un diluyente inerte como la sacarosa, lactosa o almidón. Así también puede abarcar, como una práctica normal, sustancias adicionales diferentes al diluyente inerte, e.g., agentes lubricantes como el estearato de magnesio. En el caso de las cápsulas, tabletas y píldoras, las formas de dosificaciones también pueden abarcar los agentes amortiguadores. Las tabletas y píldoras pueden adicionalmente ser preparadas con recubrimientos entéricos.

Las formas de dosificación liquida para administración oral pueden incluir emulsiones

farmacéuticamente aceptables, soluciones, suspensiones, jarabes elíxires que contienen diluyentes inertes comúnmente usados, como el agua. Tales composiciones también abarcan coadyuvantes, como agentes humectantes, emulsificaciones y de suspensión, ciclodextrinas y endulzantes saborizantes y perfumes.

Los compuestos de la presente invención también pueden ser administrados en forma de liposomas. Como se sabe estas son generalmente formadas por cristales líquidos hidratados, mono o multi laminares, dispersos en un medio acuoso. Cualquier lípido no tóxico, aceptable fisiológicamente y metabolizable capaz de formar liposomas puede ser usado en las presentes composiciones en forma de liposomas que pueden contener, en adición a los compuestos de la presente invención, estabilizadores preservativos excipientes y similares. Los lípidos preferidos son los Fosfolípidos y la Fosfatidinilcolina (lecitinas), tanto naturales como sintéticas.

Métodos para formar liposomas son conocidos en el estado del arte. Ver por ejemplo Prescott, Ed., Methods in Cell Biology, Volumen XIV, Academic Press,New York,N.W.,p.33 et seq (1976).

Mientras los compuestos de la invención pueden ser administrados como el agente farmacéutico activo exclusivo, también pueden ser usados en combinación con uno o más agentes usados en el tratamiento del cáncer. Los agentes representativos utilizados en combinación con los compuestos de la invención para el tratamiento del cáncer incluyen por ejemplo, idinotecan , topotecan, gencitabina, 5- fluoracil, leucovoril, carboplatil, cisplatin, taxanos, tezacitabina, ciclofosfamida, alcaloides vinca, imatinib (Gleevec), antraciclinas, rituximab, trastuzumab, así como otros agentes de quimioterapia para el cáncer.

Los compuestos de arriba pueden ser empleados en combinación con los compuestos de la invención que serán usados en cantidades terapéuticas como está indicado en el

Physician's Desk Reference (PDR) 47th Edition (1993), lo cual es incorporado aquí como referencia o en cantidades terapéuticamente usadas como deberían saber los expertos en el arte.

Los compuestos de la invención y los otros agentes anticáncer pueden ser administrados en la dosis clínica máxima recomendada o en bajas dosis: Los niveles de dosificación de los compuestos activos en las composiciones de la invención pueden ser variados tanto así que para obtener una respuesta terapéutica deseada dependen de la ruta de administración, severidad de la enfermedad y la respuesta del paciente. La combinación puede ser administrada como composiciones separadas o como una forma de dosificación sencilla que contiene ambos agentes. Cuando es administrada como una combinación, los agentes terapéuticos pueden ser formulados como composiciones separadas, las cuales son suministradas al mismo o a diferente tiempo, o los agentes terapéuticos, pueden ser suministrados como una composición sencilla.

Antiestrógenos, tales como talmoxifen, inhiben el crecimiento del cáncer de pecho a través de la inducción de la detección del ciclo celular que requiere la acción del inhibidor del ciclo celular p27Kip. Recientemente ha sido demostrado que la ruta de la activación de la Quinaza Ras-Raf- MAP altera el estado de fosforilación del p27Kip tal que su actividad inhibitoria detiene el ciclo celular y este es atenuado, por lo tanto, contribuyendo a la resistencia del antiestrógeno. (Donovan et al,J.Biol.Chem.276:40888, 2001). Como está reportado por Donovan et, al; la inhibición del Señalante MAPK. a través del tratamiento con el inhibidor MEK cambia el estado de fosforilación del p27Kip en la hormona refractoria de las líneas celulares del cáncer de pecho y restaurando de la sensibilidad hormonal. En este sentido, los compuestos de las Fórmulas (I), (II), (III), (IV) y (V) pueden ser usados en el

tratamiento hormonal dependiente del tipo de cáncer, tal como el de pecho y el de próstata. Para revertir la resistencia hormonal comúnmente es tratado este tipo de cánceres con agentes anticánceres convencionales.

En los cánceres hematológicos tales como la Leucemia Mielogenosa Crónica (CML), la traslocación cromosómica es responsable por la constitutivamente activada Quinaza Tiroxina BCR-AB1. Los pacientes afligidos responden al Gleevec, una pequeña molécula del inhibidor Quinaza Tiroxina, como un resultado de la inhibición de la actividad de la Quinaza AB1. Sin embargo, muchos pacientes con avanzadas etapas de enfermedad responden al Gleevec inicialmente pero luego recaen más tarde debido a las mutaciones de la resistencia conferida en el dominio de la Quinaza AB1. Estudios *in vitro* han demostrado que BCR-AB1 emplea la ruta de la Quinaza Raf para acrecentar sus efectos. Además, inhibir más de una Quinaza en la misma ruta provee protección adicional contra dichas mutaciones. De acuerdo con otro aspecto de la invención los compuestos de Fórmula (I), (II), (III), (IV) y (V) son usados en combinación con, al menos, un agente adicional, tal como el Gleevec en el tratamiento de los cánceres hematológicos tales como Leucemia Mielogenosa Crónica (CML), para revertir o prevenir la resistencia a, al menos, un agente adicional.

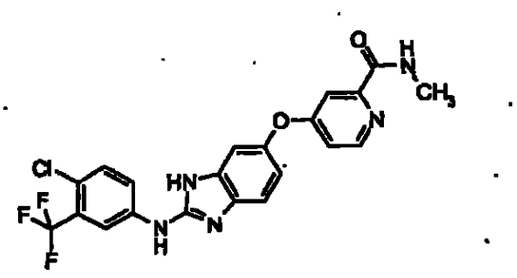
La presente invención será entendida más adecuadamente con referencia a los siguientes ejemplos, los cuales están provistos a modo de ilustración y no tienen la intención de limitar la presente invención.

Ejemplo 1

Síntesis of 4-[(2-{[4-cloro-3-(trifluorometil)fenil] amino}-

1H-bencimidazol-6-y1)oxy] -N- metilpiridina-2-carboxamida

La composición 4-[(2-{[4cloro-3-(triflurometil)fenil]amino}-1H-bencimidazol-6-y1)oxy]-N-metilpiridina-2-carboxamida fue Sintetizado como sigue:



Paso 1: Síntesis de 4-[(4-amino3-nitrofenil)oxi]-*N*-metilpiridina -2-carboxamida:

Una mezcla contiene 4-amino-3-nitrofenol- (1eq) y bis(trimetilsilil)amida de potasio fue agitada en dimetilformamida por 2 horas a temperatura ambiente. A esta mezcla le fue añadida (4-cloro(2-piridil))-*N*-metilcarboxamida (1eq) y carbonato de potasio (1.2eq) y agitada a 90°C por 3 días. La mezcla reaccionante fue luego concentrada y dividida entre etil acetato y agua. La capa orgánica fue separada y lavada con salmuera, secada, filtrada y concentrada en vacío para dar un sólido castaño. La purificación sobre silica gel (2% trietil amina / 50% acetato de etílo en hexano) dió 4-[(4-amino-3-nitrofenuçil)oxi]-*N*-metilpiridina-2-carboxamida como un sólido naranja. El producto fue satisfactorio NMR. HPLC, 3.39 min; MS: MH+ = 289.

Paso 2: Síntesis del 4-[(3,4-diaminofenil)oxí]-N-metilpiridina-2-carboxamida. La mezcla contiene [4-(3-amino-4-nitrofenoxy)(2-pirinil)]-N- en metanol con cantidad catalítica de 10%Pd/C el cual fue hidrogenado hasta que desapareció el color amarillo para dar el producto amina. HPLC, 2,5 mins; MS: MH+=259.

Paso 3: síntesis de 4-[(2-{[4-cloro-3(trifuormetil)fenil]amino}-1H-bencimidazol-6-

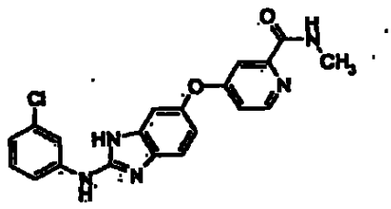
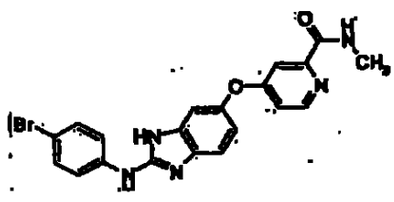
il)oxy]-N-metilpiridina-2-carboxamida:

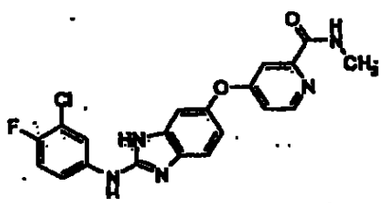
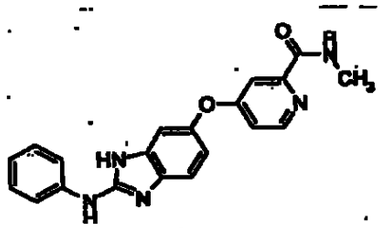
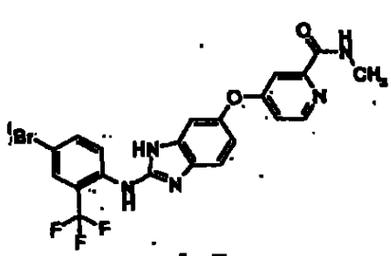
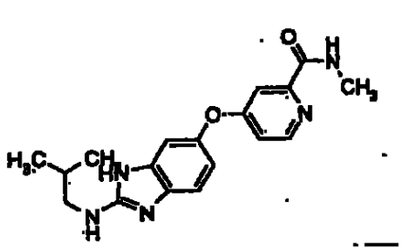
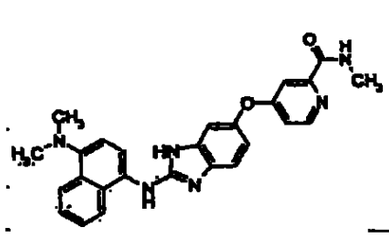
La mezcla conteniendo 4-[(3,4 diaminofenil)oxy]-N-metilpiridina-2-carboxamida (1eq) y 4-cloro-3-(trifluormetil)bencenoisotiocinato (1eq) en tetrahidrofurano la cual fue agitada a temperatura ambiente por 16 horas para dar la correspondiente tioúrea. A la mezcla resultante le fue añadido 1-etil-3-(3-dimetoilaminopropil)carbodiimida hidrocloruro (2eq) y la mezcla fue agitada por otras 10 horas. La mezcla fue concentrada y dividida entre acetato de etilo y agua. La capa orgánica fue lavada con salmuera y secada. La purificación sobre HPLC dió 4-[(2-{[4-cloro-3-(trifluormetil)fenil]amino}-1H-bencimidazol-6-il)oxy]-*N*-metil-piridina-2-carboxamida. MS: MH+ = 462.

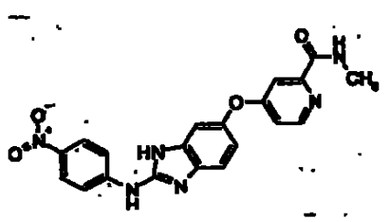
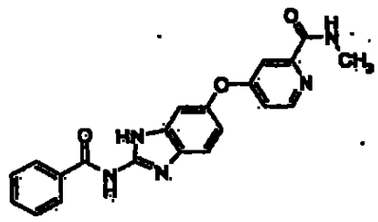
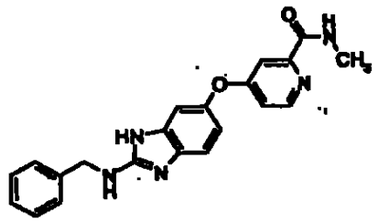
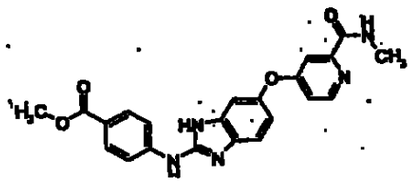
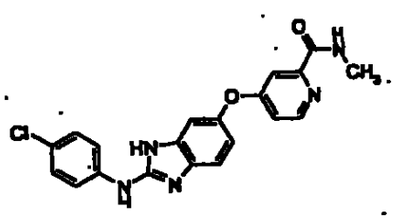
Ejemplo 2-108

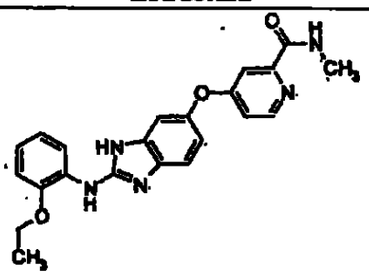
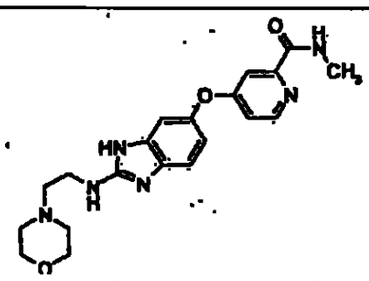
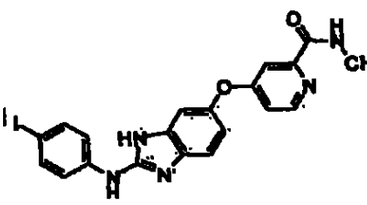
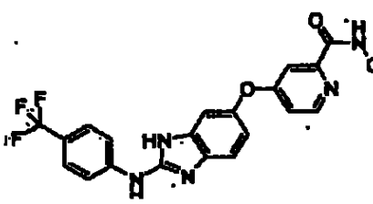
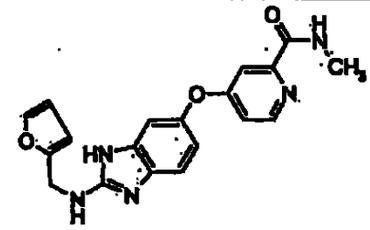
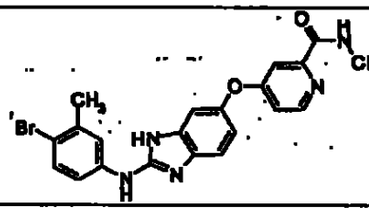
Los compuestos mostrados la siguiente Tabla 1 (Ejemplos 2-108) fueron preparados a partir del procedimiento descrito para el Ejemplo 1.

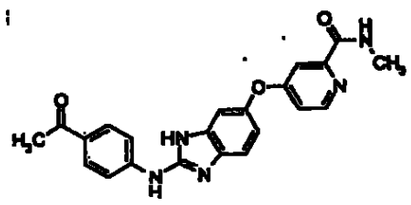
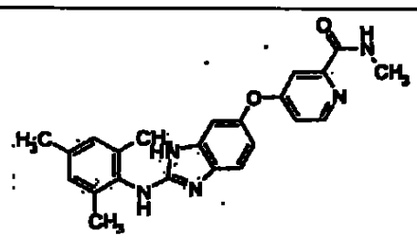
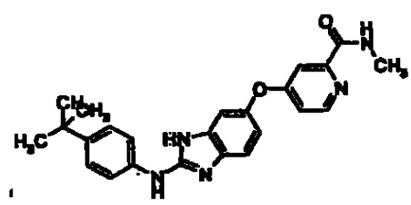
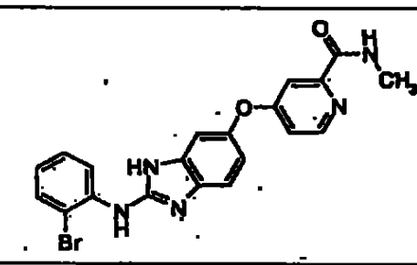
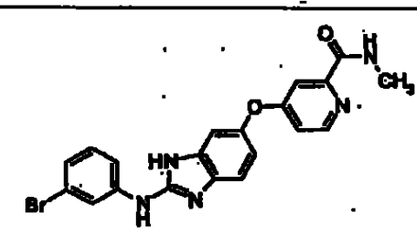
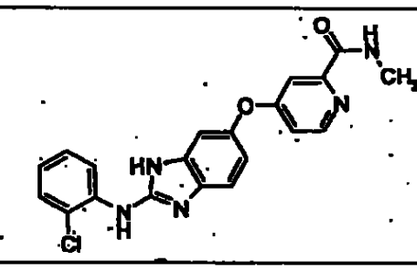
Tabla 1

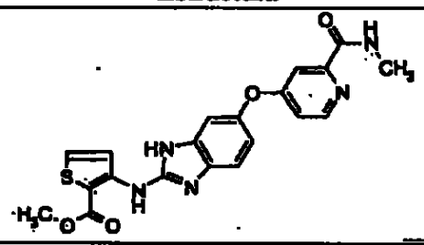
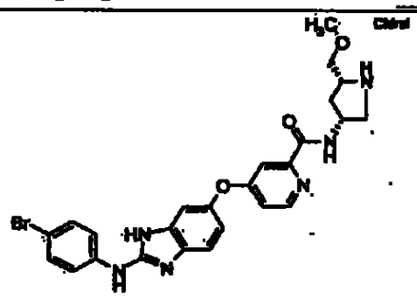
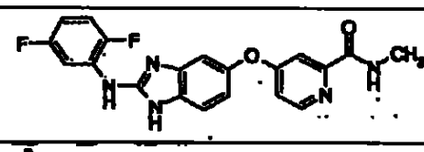
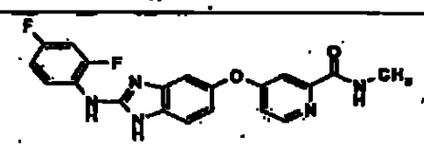
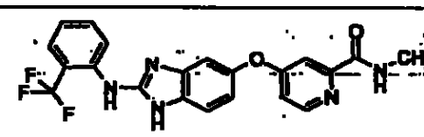
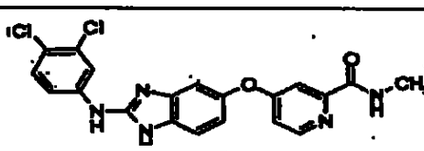
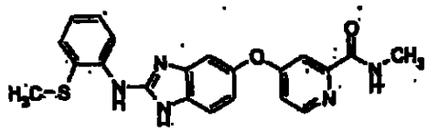
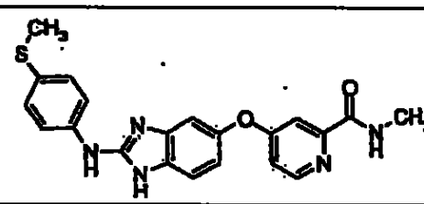
Ejemplo	Estructura	Nombre	MH+
2		4-({2-[(3-clorofenil)amino]-1H-bencimidazol-6-il}oxi)-N-metil-piridin-2-carboxamida	394
3		4-({2-[(4-bromofenil)amino]-1H-bencimidazol-6-il}oxi)-N-metilpiridin-2-carboxamida	440

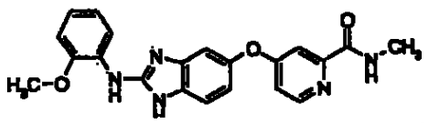
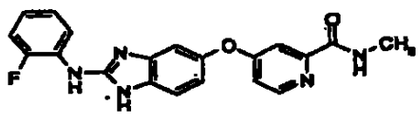
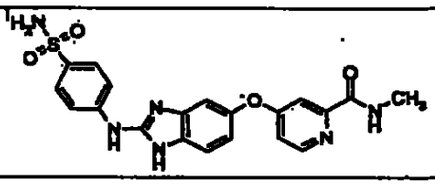
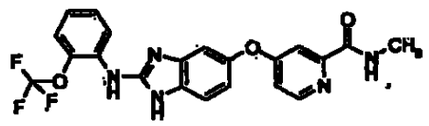
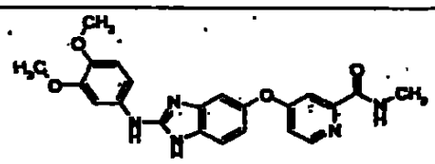
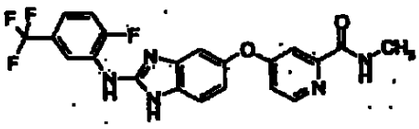
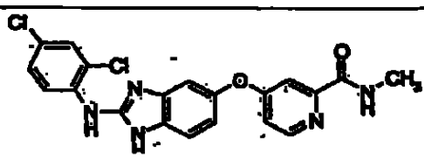
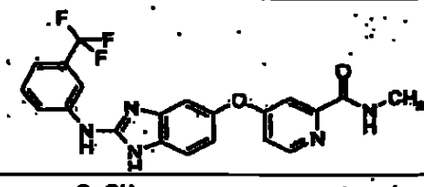
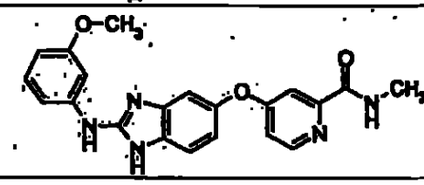
Ejemplo	Estructura	Nombre	MH+
4		4-({2-[(3-cloro-4-fluorofenil)amino]-1H-bencimidazol-6-il}oxi)-N-metilpiridin-2-carboxamida	412
5		N-metil-4-{[2-(fenilamino)-1H-bencimidazol-6-il]-oxi}-piridin–2–carboxamida	360
6		4-[(2-{[4-bromo-2-(trifluorometil)fenil]amino}-1H-bencimidazol-6-il)oxi]-N-metil-piridin-2-carboxamida	508
7		N–metil1-4-({2-[(2-metilpropyl)-amino]-1H-bencimidazol-6-il}-oxi)piridin-2-carboxamida	340
8		4-[(2-{[4-(dimetilamino)-naftalen-1-il] amino}-1H-bencimidazol-6-il)oxi]-N-metil-piridin-2-carboxamida	453

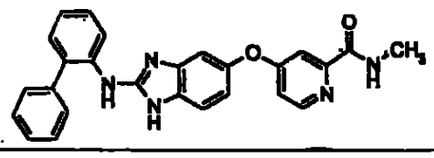
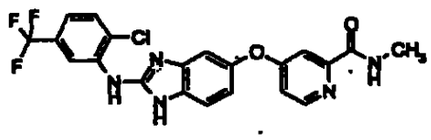
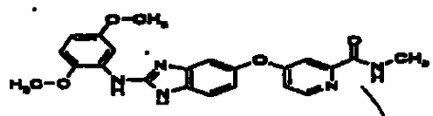
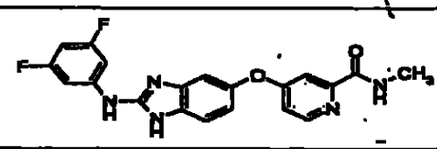
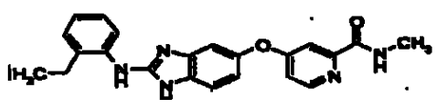
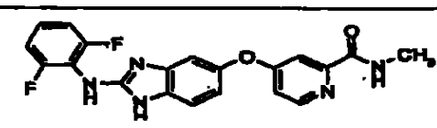
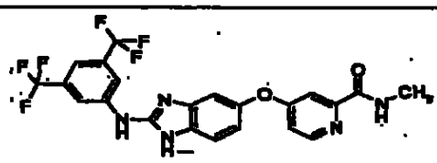
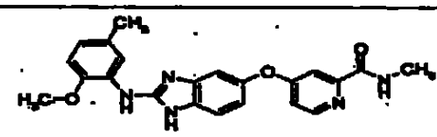
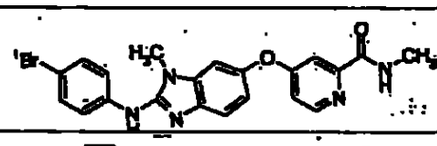
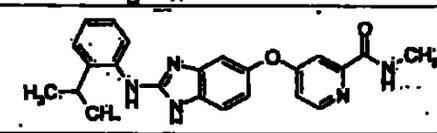
Ejemplo	Estructura	Nombre	MH+
9		N-metil-4-({2-[(4-nitrofenil)-amino]-1H-bencimidazol-6-il}-oxi) piridin – 2 –carboxamida	405
10		N-metil-4-({2-[(fenilcarbonil)-amino]- 1H-bencimidazol-6-il}-oxi) piridin – 2 –carboxamida	388
11		N-metil-4-({2-[(fenilmetil)-amino]-1H-bencimidazol-6-il}-oxi) piridin – 2 –carboxamida	374
12		Metil-4-{[6-({2-[(metilamino)-carbonil] piridin-4-il}oxi)-1H-bencimidazol-2-il]amino} benzoato	418
13		4-({2-[(4-clorofenil) amino]-1H-bencimidazol-6-il}ox)-N-metil-piridin – 2- carboxamida	394

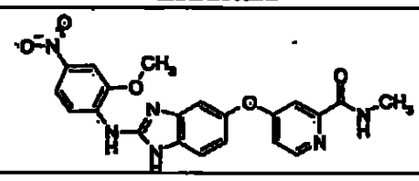
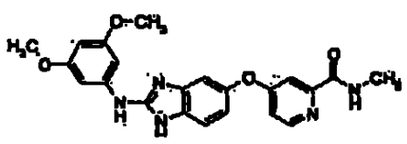
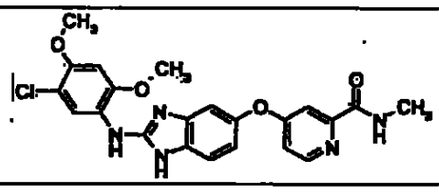
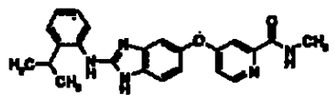
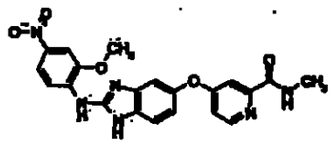
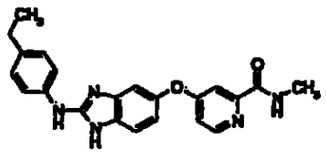
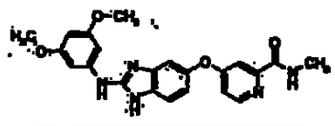
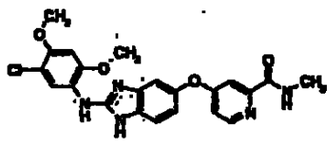
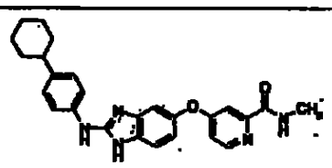
Ejemplo	Estructura	Nombre	MH+
14		4-[(2-{[2-(etiloxi)fenil]-amino}-1H-bencimidazol-6-il)-oxi]-N-metilpiridin-2-carboxamida	404
15		N-metil-4-({2-[(2-morfolin-4-iletil) amino]-1H-bencimidazol-6-il}oxi] piridin-2-carboxamida	397
16		4-({2-[(4-iodofenil) amino]-1H-bencimidazol-6-il}oxi-N-metil-piridin-2-carboxamida	486
17		N-metil-4-[(-2{[4-(trifluorometil) fenilamino}-1H-bencimidazol-6-il) oxi] piridin-2-carboxamida	428
18		4-({2-[(furan-2-ilmetil)amino]-1H-bencimidazol-6-il}oxi)-N-metilpiridin-2-carboxamida	364
19		4-({2-[4-bromo-3-metilfenil)-amino]- 1H- bencimidazol-6-il}oxi)-N-metilpiridin-2-carboxamida	453

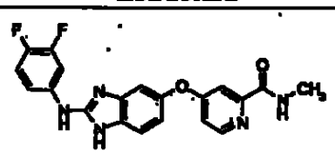
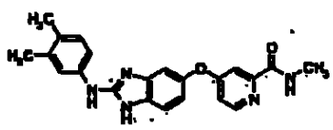
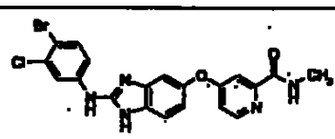
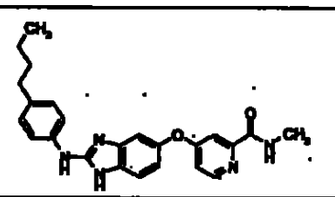
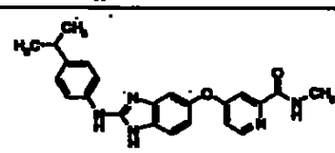
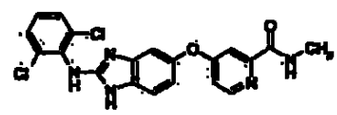
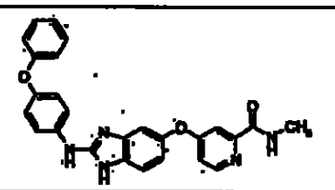
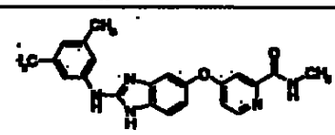
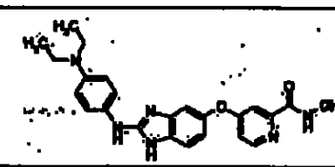
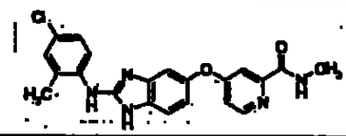
Ejemplo	Estructura	Nombre	MH+
20		4-({2-[(4-acetilfenil)amino]-1H-bencimidazol-6-il}oxi)-N-metil-piridin-2-carboxamida	402
21		N-metil-4-({2-[(2,4,6-trimetil-fenil) amino]-1H-bencimidazol-6-il}oxi) piridin – 2 carboxamida	402
22		4-[(2-{[4-(1,1-dimetiletil)-fenil] amino}-1H-bencimidazol-6-il)oxi]-N –metilpiridin-2-carboxamida	416
23		4-({2-[(2-bromofenil)amino]- 1H-bencimidazol-6-il)oxi]-N – metilpiridin-2-carboxamida	440
24		4-({2-[(3-bromofenil)amino]- 1H-bencimidazol-6-il)oxi]-N – metilpiridin-2-carboxamida	440
25		4-({2-[(2-clorofenil)amino]- 1H-bencimidazol-6-il)oxi]-N – metilpiridin-2-carboxamida	394

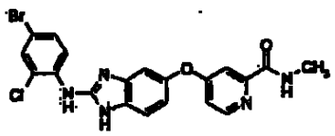
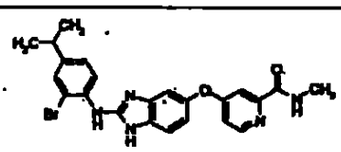
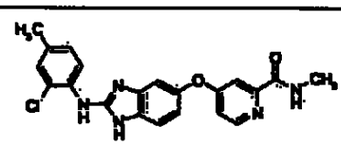
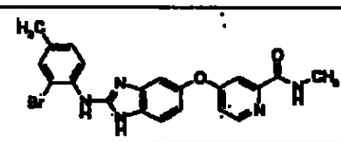
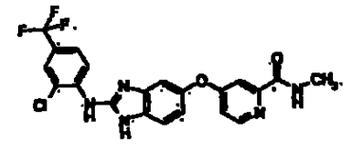
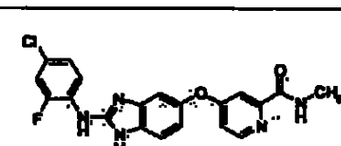
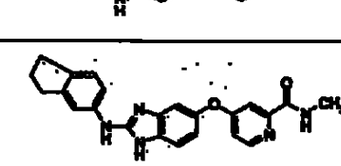
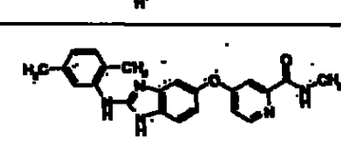
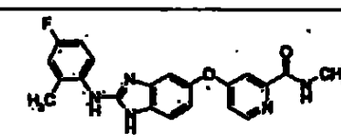
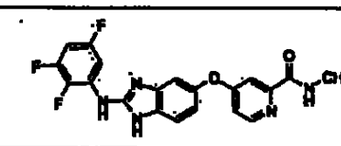
Ejemplo	Estructura	Nombre	MH+
26		Metil3-{[6-({2-[(metilamino)-carbonil] piridin-4-il}oxi)-1H-bencimidazol-2-il] amino}-tiofen-2-carboxilato	424
27		4-({2-[(4-bromofenil)amino]-1H-bencimidazol-6-il}oxi)-N-{(3R,5R)- 5-[(metiloxi)metil]-pirrolidin-3-il} piridin-2-carboxamida	539
28		(4-{2-[(2,5-difluorofenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	395.3
29		(4-{2-[(2,4-difluorofenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	395.3
30		N-metil[4-(2-{[2-(trifluoro-metil)fenil] amino}-bencimidazol-5-iloxi)(2-piridil)]-carboxamida	427.3
31		4(4-{2-[(3,4-diclorofenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	428.2
32		N-metil(4-{2-[(2-metiltiofenil)amino] bencimidazol-5-iloxi}(2-piridil)) carboxamida	405.4
33		N-metil(4-{2-[(4-metiltiofenil)amino] bencimidazol-5-iloxi}(2-piridil)) carboxamida	

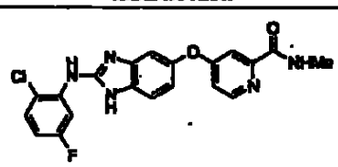
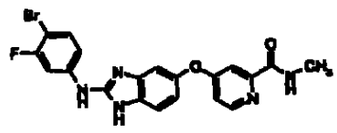
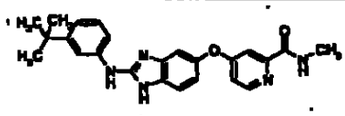
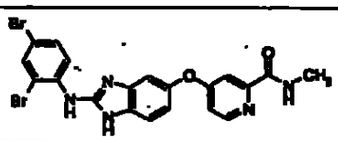
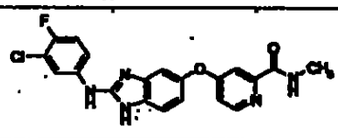
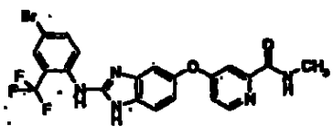
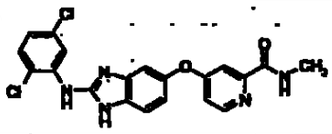
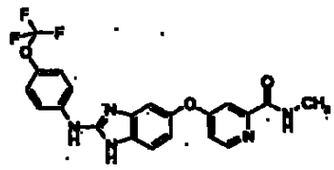
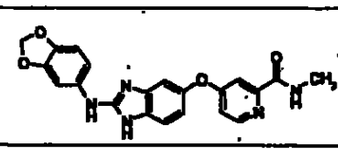
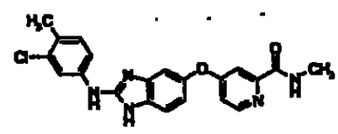
Ejemplo	Estructura	Nombre	MH+
34		(4-{2-[(2-metoxifenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	389.4
35		(4-{2-[(2-fluorofenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	377.3
36		N-metil(4-{-2[(4-sulfamoil-fenil) amino] bencimidazol-5-iloxi](2-piridil)) carboxamida	438.4
37		N-metil(4-{-2[(2-(trifluoro-metoxi)-fenil) amino] bencimidazol-5-iloxi](2-piridil)) carboxamida	443.3
38		(4-{2-[(3,4-dimetoxifenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	419.4
39		(4-{2-[(2-fluoro-5-(trifluoro-metil)fenil]amino]-bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	445.3
40		(4-{2-[(2,4-diclorofenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	428.2
41		N-metil(4-{-2[(3-(trifluoro-metil)-fenil) amino] bencimidazol-5-iloxi](2-piridil)) carboxamida	427.3
42		(4-{2-[(3-metoxifenil)amino]-bencimidazol-5-iloxi}(2-piridil))-N- metilcarboxamida	389.4

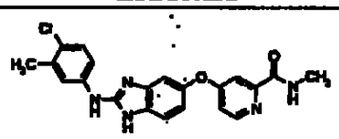
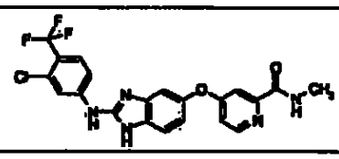
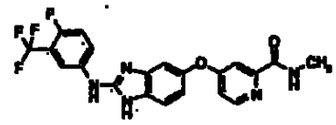
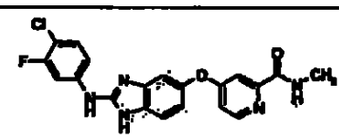
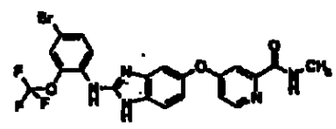
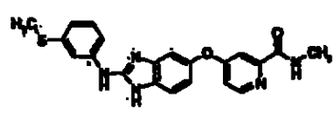
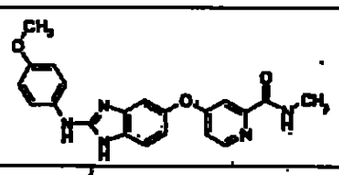
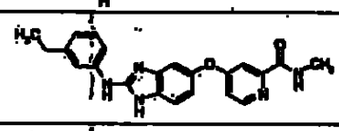
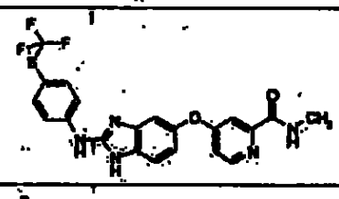
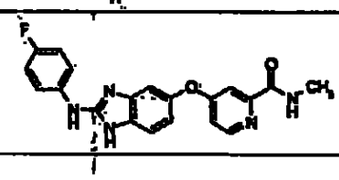
Ejemplo	Estructura	Nombre	MH+
43		N-metyl(4-{2-[(2-fenilfenil)-amino] bencimidazol-5-iloxi}(2-piridil)) carboxamida	435.3
44		[4-(2-{[2-cloro-5-(trifluoro-metil) fenil] amino}-bencimidazol-5-iloxi)(2-piridil)]N-metilcarboxamida	461.8
45		(4-{2-(2,5-dimetoxifenil)-amino] bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	419.4
46		(4-{2-[(3,5-difluorofenil)-amino] - bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	395.3
47		(4-{2-(2-etilfenil)-amino] bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	387.4
48		(4-{2-[(3,5-difluorofenil)-amino] - bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	395.4
49		[4-(2-{[3,3-Bis(trifluoro-metil) fenil] amino}-bencimidazol-5-iloxi)(2-piridil)]N-metilcarboxamida	495.4
50		(4-{2-[(2-metoxi-5-metilfenil)amino]- bencimidazol – 5-iloxi}2-piridil))-N-metilcarboxamida	403.4
51		(4-{2-[(4-bromofenil)amino]-1-metil- bencimidazol – 6-iloxi}2-piridil))-N-metilcarboxamida	452.3
52		N-metil[4-(2-{[2-(metiletil)-fenil] amino} bencimidazol-5-iloxi)(2-piridil)] carboxamida	401.4

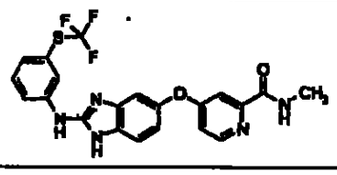
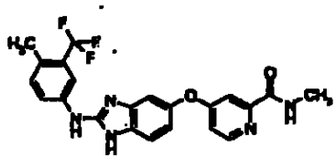
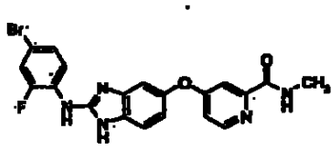
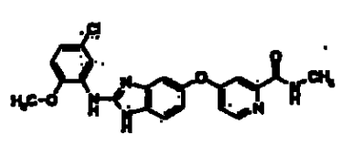
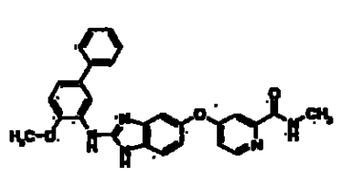
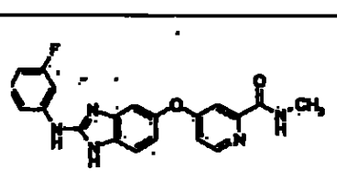
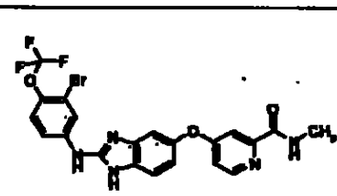
Ejemplo	Estructura	Nombre	MH+
53		(4-{2-[(2-metoxi-4-nitrofenil)-amino] bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	434.4
54		(4-{2-[(3,5-dimetoxifenil)-amino] bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	420.1
55		(4-{2-[(5-cloro-2,4-dimetoxifenil)-amino] bencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	454.1
56		N-metil-4-[(2-{[2-(1-metil-etil) fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	402.5
57		N-metil-4-[(2-{[2-(metiloxi)-4-nitrofenil]amino}-1H-bencimidazol-5-il)oxi] piridin-2-carboxamida	435.4
58		4-({2-[(4-etilfenil)amino]-1H-bencimidazol-5-il}oxi)}N-metilpiridin- 2-carboxamida	388.4
59		4-[(2-{[3,5-Bis(metiloxi)fenil]-amino}-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	420.4
60		4-[(2-{[5-cloro-2,4-Bis(metiloxi)fenil]-amino}-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	454.9
61		4-({2-[(4-ciclohexilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin -2-carboxamida	442.5

Ejemplo	Estructura	Nombre	MH+
62		4-({2-[(3,4-diflurofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin -2-carboxamida	396.4
63		4-({2-[(3,4-dimetilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	388.4
64		4-({2-[(4-bromo-3-clorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	463.7
65		4-({2-[(4-butilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	416.5
66		N-metil-4-[(2-{[4-(1-metil-etil)fenil] amino}-1H-bencimidazol-5-il)oxi] piridin-2-carboxamida	402.5
67		4-({2-[(2,6-diclorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	429.3
68		N-metil-4-[(2-{[4-(feniloxi)-fenil] amino}-1H-bencimidazol-5-il)oxi] piridin-2-carboxamida	452.5
69		4-({2-[(3,5-dimetilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	388.4
70		4-[(2-{[4-(dietilamino) fenil]-amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	431.5
71		4-({2-[(4-cloro-2-metilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	408.9

Ejemplo	Estructura	Nombre	MH+
72		4-({2-[(4-bromo-2-clorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	473.7
73		4-[(2-{[2-bromo-4-(1-metil-etil) fenil]-amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	481.4
74		4-({2-[(2-cloro-4-metilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	408.9
75		4-({2-[(2-bromo-4-metilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	453.3
76		4-[(2-{[2-cloro-4-(trifluoro-metil) fenil]-amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	462.8
77		4-({2-[(4-cloro-2-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin –2-carboxamida	412.8
78		4-{[2-(2,3-dihidro-1H-inden-5-ilamino)-1H-bencimidazol-5-il]-oxi}-N-metilpiridin-2-carboxamida	400.5
79		4-({2-[(2,5-dimetilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	388.4
80		4-({2-[(4-fluoro-2-metilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	392.4
81		N-metil-4-({2-[(2,3,5-trifluoro-fenil) amino]1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	414.4

Ejemplo	Estructura	Nombre	MH+
82		4-({2-[(2-cloro-5-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	412.8
83		4-({2-[(4-bromo-3-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	457.3
84		4-[(2-{[3-(1,1-dimetiletil)-fenil] amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	416.5
85		4-({2-[(2,4-dibromofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	518.2
86		4-({2-[(3-cloro-4-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	412.8
87		4-[(2-{[4-bromo-2-(trifluoro-metil)-fenil] amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	507.3
88		4-({2-[(2,5-diclorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	429.3
89		N-metil-4-{[2-({4-[trifluoro-metil)oxi] fenil}amino)-1H-bencimidazol-5-il] oxi}piridin-2-carboxamida	444.4
90		4-{[2-(1,3-benzodioxol-5-il-amino)-1H-bencimidazol-5-il]-oxi}-N-metilpiridin-2-carboxamida	404.4
91		4-({2-[(3-cloro-4-metilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	408.9

Ejemplo	Estructura	Nombre	MH+
92		4-({2-[(4-cloro-3-metilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	408.9
93		4-[(2-{[3-cloro-4-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metil-piridin-2-carboxamida	462.8
94		4-[(2-{[4-fluoro-3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metil-piridin-2-carboxamida	446.4
95		4-({2-[(4-cloro-3-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	412.8
96		4-{[2-({4-bromo-2-[(trifluoro-metil)oxi]fenil}amino)-1H-bencimidazol-5-il]oxi}-N-metil-piridin-2-carboxamida	523.3
97		N-metil-4-[(2-{[3-(metiltio)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	406.5
98		N-metil-4-[(2-{[4-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	390.4
99		4-({2-[(3-etilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metil-piridin-2-carboxamida	388.4
100		N-metil-4-{[2-({4-[(trifluorormetil)tio]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	460.4
101		4-({2-[(4-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metil-piridin-2-carboxamida	378.4

Ejemplo	Estructura	Nombre	MH+
102		N-metil-4-{[2-({3-[(trifluorormetil)tio]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	460.4
103		N-metil-4-[(2-{[4-metil-3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	442.4
104		4-({2-[(4-bromo-2-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	457.3
105		4-[(2-{[5-cloro-2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	424.9
106		N-metil-4-[(2-{[4-(metiloxi)-1,1'-bifenil-3-il]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	466.5
107		4-({2-[(3-fluorofenil)-amino]-1H-bencimidazol-5-il}-oxi)-N-metil-piridin-2-carboxamida	378.4
108		4-{[2-({3-bromo-4-[(trifluoro-metil)oxi]fenil}amino)-1H-bencimidazol-5-il]oxi}-N-metil-piridin-2-carboxamida	523.3

Ejemplo 109

Síntesis de (4-{2-[(4-bromofenil)amino]-benzotiazol-5-iloxi}(2-piridil))-N-metilcarboxamida

Paso 1: Síntesis de 2-bromo-5-metiloxibenzotiazol

Una solución de bromo (3.6eq) en cloroformo (.75mL) fue añadida a cuentagotas durante un periodo de una hora a una suspensión agitada de 5-metoxi-2-mercaptobenzotiazol (1eq) en cloroformo a 0°C. La mezcla fue agitada por 30 minutos antes que le fuera añadida agua lentamente y agitada por 20 minutos más. La mezcla fue filtrada para remover una crema sólida. La fase orgánica fue secada y evaporada para dejar un sólido café. Dicho sólido fue disuelto en éter y filtrado. El residuo fue lavado con éter y el filtrado junto con el primero fueron combinados y evaporados, pasados por el cromatógRafo (4:1 hexanos y acetato de etilo) para dar de 2-bromo-5-metiloxibenzotiazol como un sólido amarillo pálido. MS: MH+ = 244.

Paso 2: Síntesis de (4-bromofenil)(5-metoxibenzotiazol-2-il)amina.

La mezcla que contiene 2-bromo-5-metoxibenzotiazol (1eq), 4-bromoanilina (2q) y diisopropiletilamina fueron colocados en un horno micro-ondas en NMP a 220°C. La mezcla resultante fue concentrada y dividida entre acetato de etilo y agua. La capa orgánica fue lavada con salmuera y secada. La purificación sobre sílica gel dió (4-bromofenil)(5-metoxibenzotiazol-2-il)amina. MS: MH+= 335.

Paso 3: Síntesis de 2-[(4-bromofenil)amino]benzotiazol-5-ol.

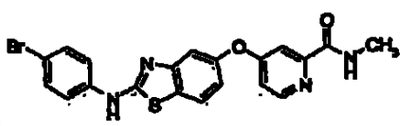
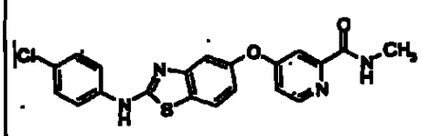
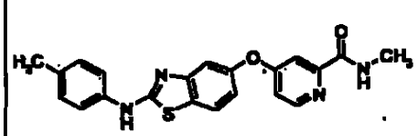
La mezcla de (4-bromofenil)(5-metoxibenzotiazol-2-il)amina y ácido hidrobrómico (48%) fue colocada en un horno micro-ondas a 150°C por 6 minutos para dar 2-[(4-bromofenil)amino]benzotiazol-5-ol. MS: MH+=321.

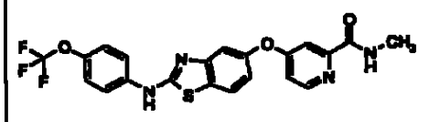
Paso 4: Síntesis (4-{2-[(4-bromofenil)amino]benzotiazol-5-iloxi}(2-piridil)) -N-metilcarboxamida.

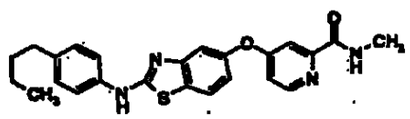
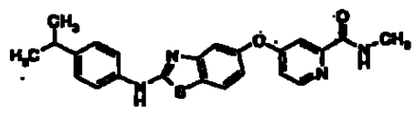
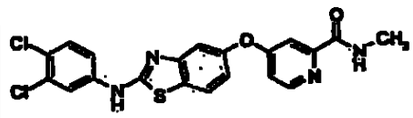
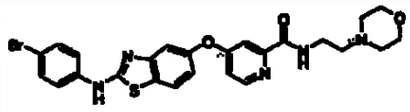
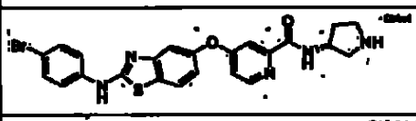
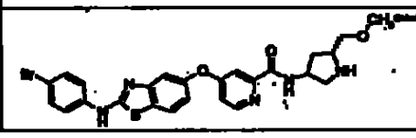
La mezcla conteniendo 2-[(4-bromofenil)amino]benzotiazol-5-ol (1eq), potasio-bis-(trimetisilil)amida (4eq) fue agitado con dimetilformamida por 30 minutos a temperatura ambiente. A esta mezcla se le agregó (4-cloro(2-piridil)-N-metilcarboxamida (1eq) y carbonato de potasio (1.2eq) luego se colocó en un horno micro-ondas por 6 minutos a 150°C. la mezcla de reacción fue entonces concentrada y dividida con acetato de etilo y agua. La capa orgánica fue separada y lavada con salmuera, secada, filtrada y concentrada. La purificación con Prep. LC (4-{2-[(4-bromofenil)amino]benzotiazol-5-iloxi}(2-piridil))-N-metilcarboxamida. MS: MH+= 455.

Cada uno de los ejemplos 110-119 mostrados en la siguiente Tabla 2 fueron sintetizados de acuerdo con los procedimientos descritos en el Ejemplo 109:

Tabla 2

Ejemplo	Estructura	Nombre	MH+
110		(4-{2-[(4-bromofenil)amino]-benzotiazol-5-iloxi}(2-piridil))-N-metilcarboxamida	455
111		(4-{2-[(4-clorofenil)amino]-benzotiazol-5-iloxi}(2-piridil))-N-metilcarboxamida	411.1
112		N-metil(4-{2-[(4-metilfenil)-amino]-benzotiazol-5-iloxi}(2-piridin))carboxamida	391.1

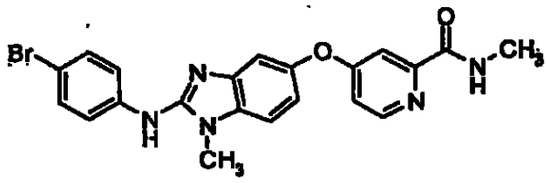
113		N-metil[4-(2-{[4-(trifluoro-metoxi)fenil]amino}-benzotiazol-5-iloxi}(2-piridin))carboxamida	461.1

Ejemplo	Estructura	Nombre	MH+
114		(4-{2-[(4-butilfenil)amino]-benzotiazol-5-iloxi}(2-piridil))-N-metilcarboxamida	433.2
115		N-metil[4-(2-{[4-(metiletil)fenil]amino}-benzotiazol-5-iloxi}(2-piridin))carboxamida	419.2
116		(4-{2-[(3,4-diclorofenil)amino]-benzotiazol-5-iloxi}(2-piridil))-N-metilcarboxamida	445
117		4-{2-[(4-bromofenil)amino]-benzotiazol-5-iloxi}(2-piridil))-N-(2-morfolin-4-iletil)-carboxamida	554.1
118		N-((3R)pirrolidin-3-il)(4-{2-[(4-bromofenil)amino]benzotiazol-5-iloxi}(2-piridil))carboxamida	510
119		N-[(3R,5R)-5-(metoximetil)-pirrolidin-3-il](4-{2-[(4-bromo-fenil)amino]benzotiazol	554.1

Ejemplo 120a

Síntesis de 4-({2-[(4-bromofenil)amino]-1-metil-1H-bencimidazol-5-yl}oxi)-N-metilpiridin-2-carboxamida

El compuesto 4-({2-[(4-bromofenil)amino]-1-metil-1H-bencimidazol-5-yl}oxi)-N-metilpiridina-2-carboxamida fue sintetizado como sigue:



Paso 1: Síntesis de 4-{[3-amino-4-(metilamino)fenil]oxi}-N- metil-piridina-2-carboxamida:

Una solución de 4-[(4-amino-3-nitrofenil)oxi]-N-metilpiridina-2-carboxamida (1eq) en cloruro de metileno fue tratada con anhídrido trifluoracético (1eq) y agitado por 10 minutos a 0°C. La mezcla fue apagada con solución saturada de $NaHCO_3$. La capa orgánica fue lavada con agua, salmuera, secada y evaporada. MS: MH+=385.2.

A una solución de trifluoracetamida (1eq) en una mezcla de tolueno, acetonitrilo y solución de hidróxido de sodio (50%) se agregó cloruro de benziltrimetilamonio (1eq) y sulfato de dimetilo (1.2eq). La mezcla bifásica fue agitada toda la noche a temperatura ambiente y evaporada. La mezcla fue recogida en acetato de etilo, lavado con agua, salmuera, secado y evaporado. El producto crudo fue purificado por cromatogRafía de columna conformada con 1:1 hexanos y acetato de etilo seguido por 2% trietilamina en 1:1 hexanos y acetato de etilo seguido por 2% trietilamina el 1:1 hexano y acetato de etil para dar N-metil-4-{[4-(metilamino)-3-nitrofenil]oxi}piridina-carboxamida como un sólido anaranjado rojizo. MS: MH+=273.3.

La solución de nitrometilamina en metanol fue trtada con paladio en carbón al 5% y agitada bajo atmósfera de nitrógeno por 15 minutos (hasta que desapareció la coloración amarilla) a temperatura ambiente. La mezcla fue filtrada y el filtrado concentrado para dar 0.36 gramos de la diamina 4-{[3-amino-4-(metilamino)fenil]oxi}-N- metil-piridina-2-carboxamida. MS:MH+=273.3

551

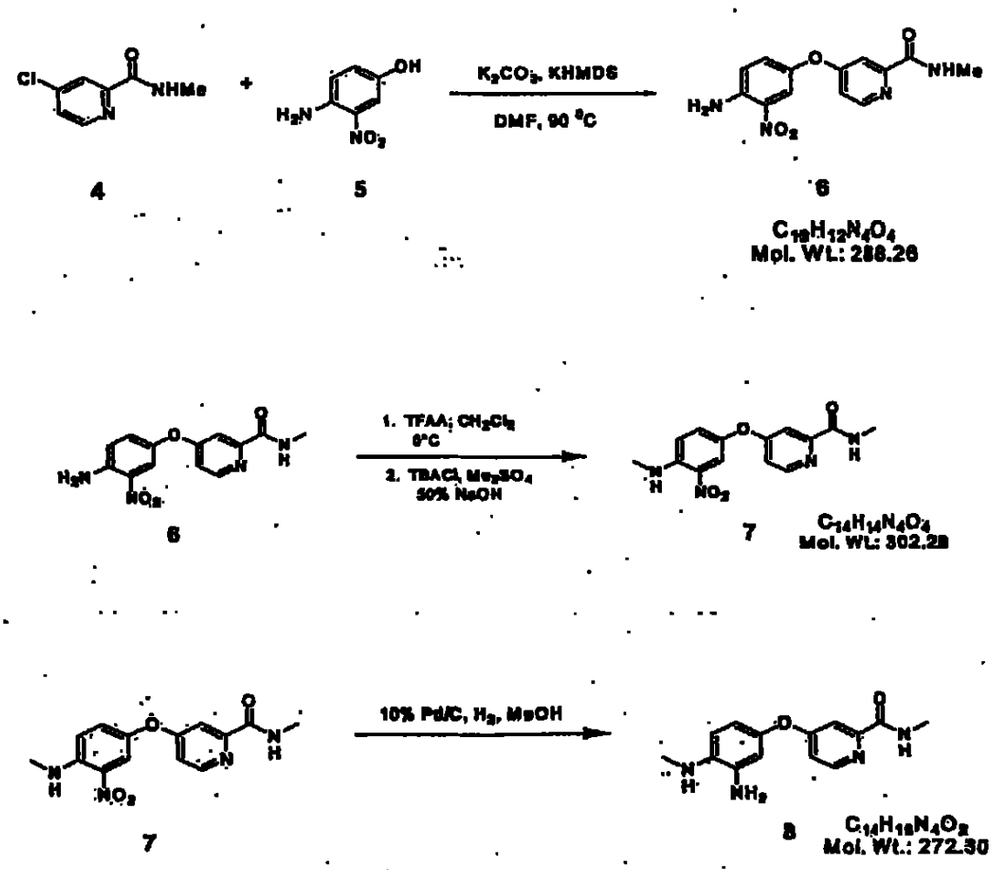
Paso 2: Síntesis de 4-({2-[(4-bromofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamide.

Una solución de diamina 4-{[3-amino-4-(metilamino)fenil]oxi}-N-metilpiridin-2-carboxamida (1eq) en metanol fue tratada con 4-bromofenil-isotiocianate (1eq) y agitada a 60°C-65° C por 2 horas. La mezcla de reacción fue enfriada bajo temperatura ambiente y añadido ioduro de metilo(1eq) y agitada toda la noche a 60° C. La reacción fue enfriada a temperatura ambiente, evaporada, recogida en acetato de etilo y lavada con agua y salmuera y evaporada bajo presión reducida. La columna de cromatogRafía usando un sistema de gradiente de solvente de hexanos y acetato de etilo y 1:1 cloruro de metileno y acetona o 5% de metanol en cloruro de metileno dió 4-({2-[(4-bromofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamide como un polvo medio blanco. MS: MH+=452.3

Ejemplo 120b

Síntesis alternativa de 4-({2-[4-bromofenil)amino]-1-metil-1H-bencimidazol-5-il}oxy)-N-metylpiridine-2-carboxamida

Paso1: Síntesis de N-metil{4-[4-(metilamino)-3-aminofenoxi] (2-piridil)}carboxamida:



Una mezcla que contiene 4-amino-3-nitrofenol 5 (1.0g, 6.4 mmol), bis(trimetilsilil)amida potasio (2.58g,12.8mmol) fue agitada en DMF (50ml) por 2 horas a temperatura ambiente. A esta mezcla fue añadido (4-cloro(2-piridil))-N-metilcarboxamida 4 (1.09 g, 6.4. mmol) y carbonato de potasio (0.5g, 7.6.mmol) y agitada a 90°C toda la noche. La mezcla de reacción fue luego concentrada y dividida entre acetato de etilo y agua. La capa orgánica fue separada y lavada con salmuera (2 x 10ml), secada, filtrada y concentrada en vacío para dar un sólido café. La purificación sobre sílica gel con 2% de trietilamina en 50% de acetato de etilo en hexano dió 1.3g (rendimiento 72%) de [4-(4amino-3nitrofenoxi)(2-piridil)]-N- metilcarboxamida 6 –como un sólido naranja: ^{1}H NMR (300MHZ, CDCL3) δ 8.40 (d, J=5.6, Hz, 1 H), 7.99 (br s, 1H), 7.90 (d,J = 2.7 Hz,1H), 7.64. (d, J=2.7 Hz), 7.17 (dd,

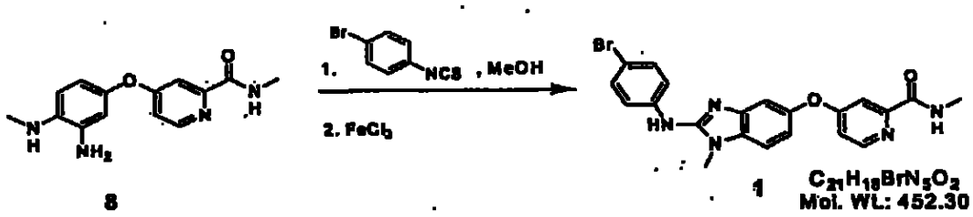
J=2.7, 9.0 Hz, 1H), 6,95 (ddd, J=0.7, 2,5, 5,6 Hz,1H), 6.89 (d, J=9.0 Hz,1H), 6.18 (br,s 2H), 3.00 (d, J=5.1 Hz, 3H);mp 208-210 °C dec; LCMS m/z 289.2 (MH),tr=1.92 min.

Un frasco de fondo redondo de tres cuellos de capacidad 500 ml con un agitador mecánico fue cargado con nitroanilina 6 (10.0 g, 34.8 mmol) y CH_2Cl_2 (175ml). La suspensión resultante fue enfriada a 0°C y TFAA (9.5 ml, 14.1g, 67.0 mmol)) fue añadido durante 16 horas mientras se permitía que el baño de refrigeración terminara. Después la reacción fue completamente analizada en el TLC[3], TBACL (5.2g, 17,5 mmol) $_4$ y dimetil sulfato (6.7 mL, 8.9 g. 70,0 mmol) fueron añadidos seguidos por 50% de solución acuosa de NaOH (140mL). La mezcla de reacción resultante fue enfriada con un baño de hielo y agitada vigorosamente durante 1.5 horas a temperatura ambiente.[3,5,6] La reacción fue luego vertida sobre agua helada y las fases resultantes fueron divididas y separadas. La fase acuosa fue extractada con cloruro de metileno (3 x 100mL) y las capas orgánicas combinadas fueron lavadas con salmuera (2 x 100 Ml), secadas (MgSO4) y concentradas. El residuo crudo fue purificado por recristalización (1:3 etanol- agua) para dar 8.36 g (27.7 mmol, 79%) de 7 como agujas rojas finas: 1H NMR (300 MHz, $CDCL_3$) δ 8.40 (dd, J=0.5,4,9 Hz, 1H), 8.07 (br d, J= 3.7 Hz, 1 H), 7,98 (br s,1H), 7.95 (d, J= 2.9 Hz, 1H), 7.62 (dd, J= 0.5,2.9 Hz, 1H), 7,27 (ddd, J=0.5, 2.9, 9.3 Hz, 1H), 6,98 (dd, J= 2.7, 5.6 Hz,1H), 6.92 (d,J= 9.3 Hz, 1H),3.07 (d,J=5.1 MHz, 3H),3.00 (d,J=5.1Hz, 3H); 13 C NMR (75 MHz, CDCL3) δ 166.6, 164.6, 152.6, 150.0, 144.8, 142.2, 130.6, 118.9, 115.5, 114.2, 109.7, 30.2, 26.4; mp 164-166°C. LCMS m/z 303.4 $(MH+)t^r$= 2.37 min.

Una suspensión de nitroanilina 7 (5.0g, 16.5 mmol) en metanol fue agitada con N_2 por 20 minutos después de los cuales 10% Pd/C (0.88g, 08. mmol) fue añadido. La reacción fue purgada con H_2 y mantenida bajo una atmósfera de H_2 toda la noche a temperatura ambiente.

La reacción fue purgada con N_2 y filtrada a través de Celita. Los sólidos recogidos fueron lavados con EtOAc (3 x50 mL), y las capas orgánicas combinadas fueron secadas ($MgSO_4$) y concentrado para refinar 4.35 g (16.0 mmol, 97%) como un sólido blanco mate 8: ^{1}H NMR (300 MHz, $CDCl_1$) δ 8.30 (d, *J* =5.5 Hz, 1 H), 7.99 (br s, 1 H), 7,67 (d, *J* =2.5 Hz, 1 H), 6.91 (dd, *J* =2.5. 5.5 Hz, 1 H), 6.62 (d, *J* =8.5 Hz, 1 H), 6.53 (dd, *J* =2.5.8.5 Hz, 1 H), 6.44 (d, *J* =2.5Hz, 1 H), 2.98 (d, *J* =5.2 Hz, 3 H), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 164.9, 152.2, 149.6, 146.0, 136.6, 136.3, 114.0, 112.3, 112.0, 110.2, 109.0, 31.6, 26.5; mp 153-156°C dec.; LCMS *m/z* 273.3 (MH^+), t_R = 1.66 min.

Paso 2: Síntesis de (4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida.



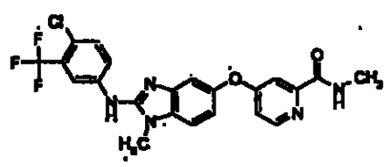
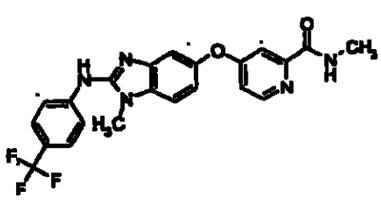
Un frasco de fondo redondo de 250 mL fue cargado con 4-bromofenilisotiocianate[1] (2.17 g, 10.1 mmol), diamina 8 (2.74 g, 10.1 mmol), y MeOH (40 mL) y la reacción fue mantenida en temperatura ambiente toda la noche. La reacción fue dividida con EtOAc (100 mL) y agua (100 mL) y filtrada a través de Celita. Las capas fueron separadas y la fase acuosa fue neutralizada (pH = 7) con solución saturada de Na_2CO_3. El resultado de la fase acuosa fue extraída con EtOAc (100 mL) y la mezcla fue filtrada a través de Celita. Las fases fueron separadas y la fase acuosa fue de nuevo extraída y filtrada. Las capas orgánicas combinadas fueron lavadas con salmuera (250 mL), secadas ($MgSO_4$) y concentradas para dar un sólido café. El residuo puro fue purificado por trituración en tolueno caliente para refinarlo 2.22 g (4.95 mmol, 49%) y dió un sólido parecido al color café claro (bronceado) 1: ^{1}H NMR

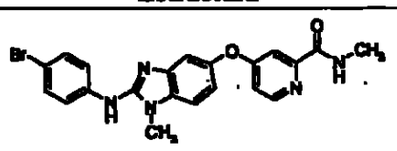
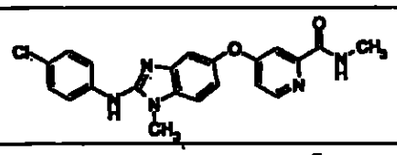
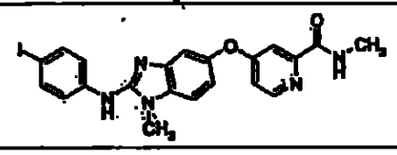
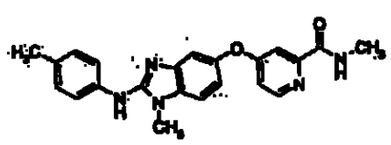
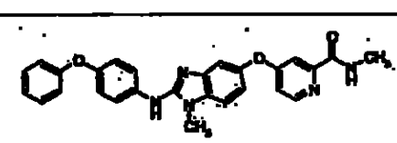
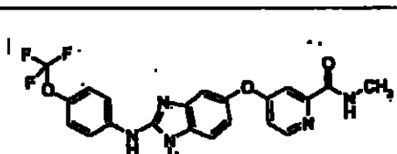
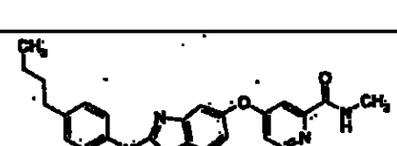
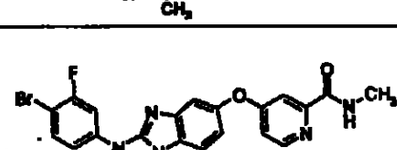
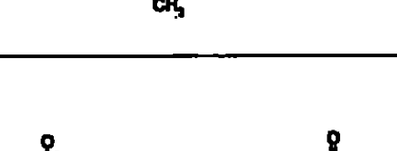
(300MHz, $CDCL_3$) δ 8.38 (d, J = 5.8 Hz, 1 H), 8.07 (br d, J = 4.7 Hz, 1 H), 7.61 (d, J = 2.5 Hz, 1 H), 7.44 (app dd, $_4$ = 8.8 Hz, 4 H), 7.05 (m, 3 H), 6.78 (dd, J = 2.2, 8.5 Hz, 1 H), 3.51 (s, 3 H), 3.00 (d, J = 5.2 Hz, 3 H); mp 251-254°C dec.; LCMS m/z 452.2 (MH^+), t_R = 2.17 min.

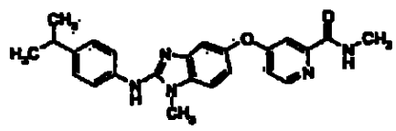
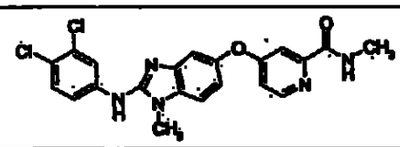
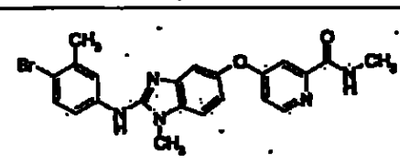
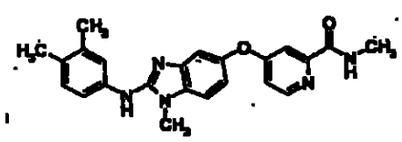
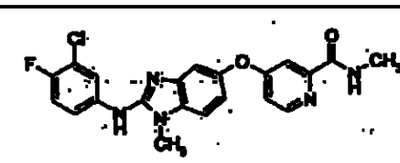
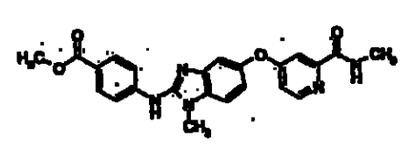
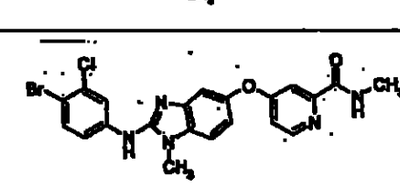
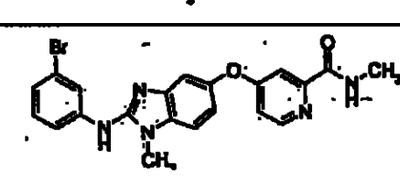
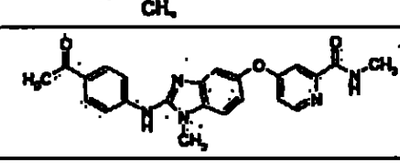
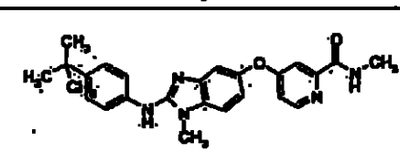
Ejemplos 121-384

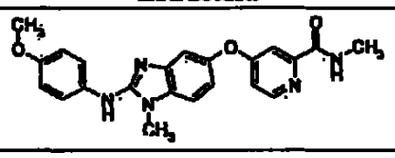
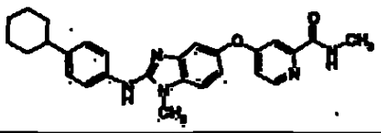
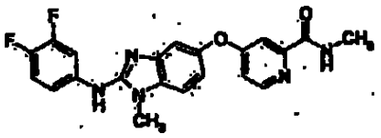
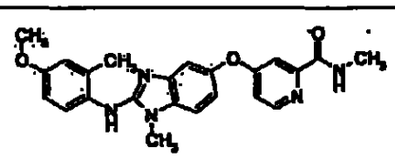
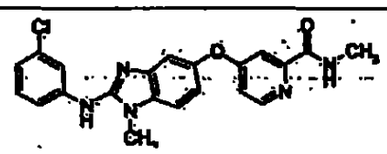
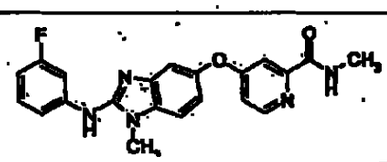
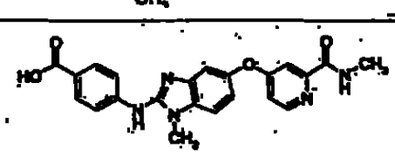
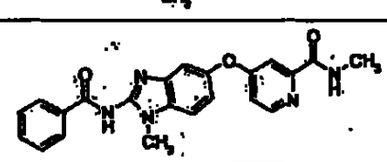
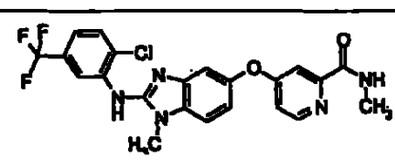
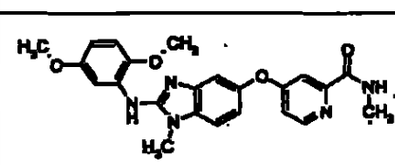
Los compuestos mostrados en la siguiente Tabla 3 (Ejemplos 121-384) fueron preparados a partir del siguiente procedimiento descrito para el Ejemplo 120a.

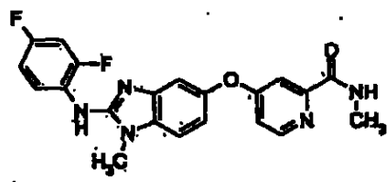
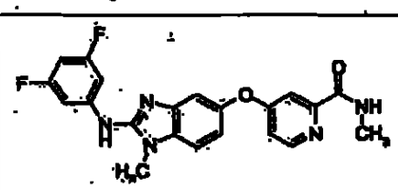
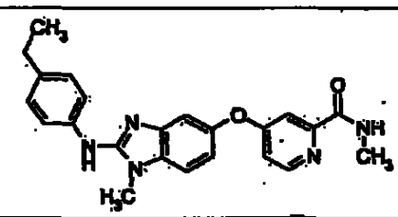
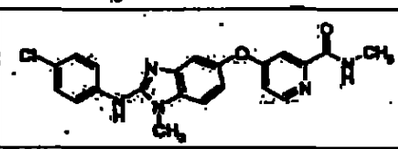
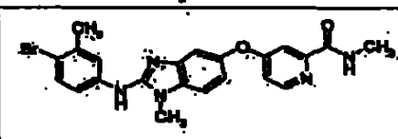
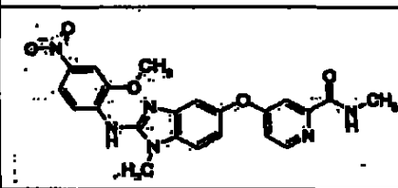
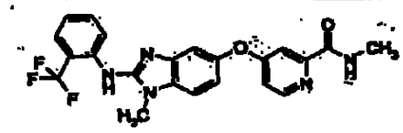
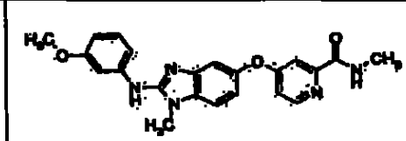
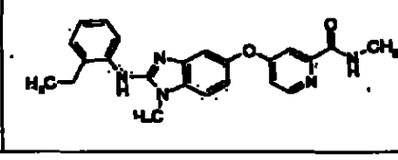
Tabla 3

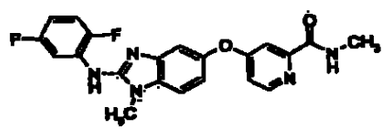
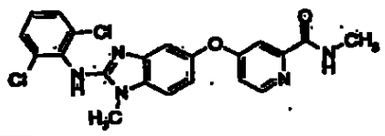
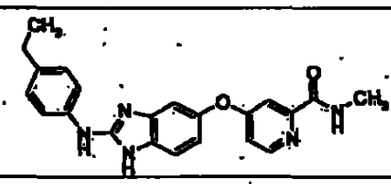
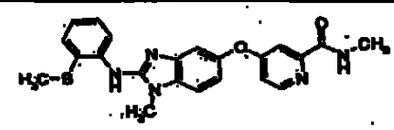
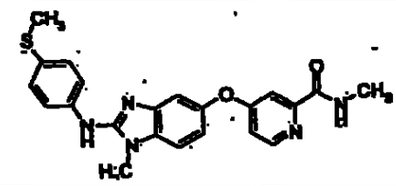
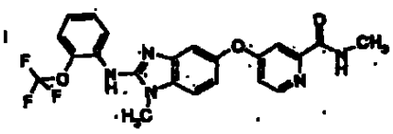
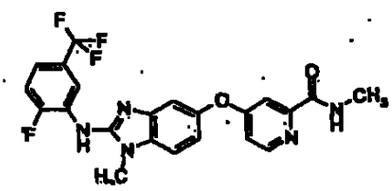
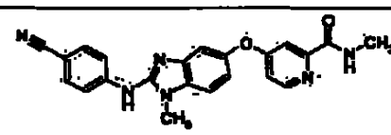
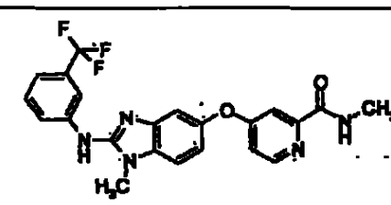
Ejemplo	Estructura	Nombre	MH+
121		4-[(2-{[4-cloro-3-(trifluoro-metil)fenil] amino)-1-metil-1H-bencimidazol-5-il) –oxi]-N-metilpiridin-2-carboxamida	476.1
122		N-metil-4-[(1-metil-2-{[4-(trifluorometil)fenil] amino}1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	442

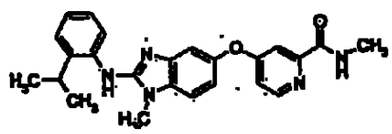
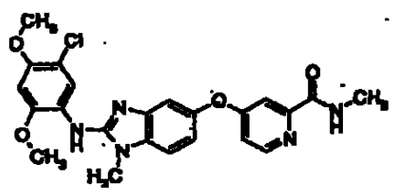
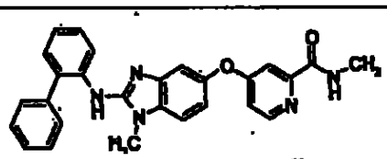
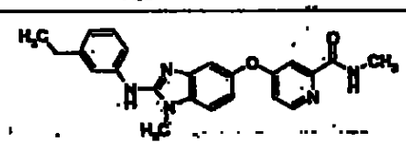
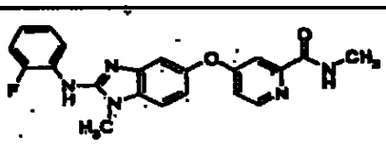
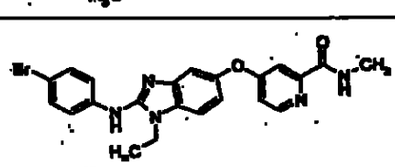
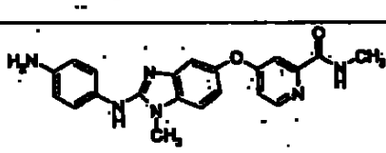
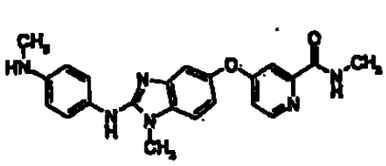
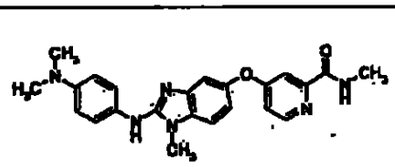
Ejemplo	Estructura	Nombre	MH+
123		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	452.0
124		(4-{2-[(4-clorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	408.1
125		(4-{2-[(4-iodofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	500.1
126		N-metil(4-{1-metil-2-[(4-metilfenil) amino]bencimidazol-5-iloxi})2-piridil))carboxamida	388.2
127		N-metil(4-{1-metil-2-[(4-fenoxifenil) amino]bencimidazol-5-iloxi})2-piridil))carboxamida	466.2
128		N-metil[4-(1-metil-2-{[4-(trifluorometoxi)fenil]amino} bencimidazol-5-iloxi)(2-piridil)]carboxamida	458.2
129		(4-{2-[(4-butilfenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	430.2
130		(4-{2-[(4-bromo-3-fluorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	470.1
131		N-metil(4-{1-metil-2-[(4-nitrofenil) amino]bencimidazol-5-iloxi})2-piridil))carboxamida	419.2

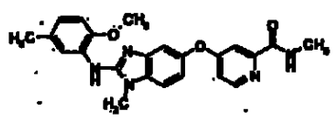
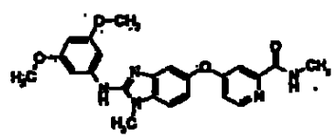
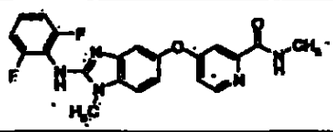
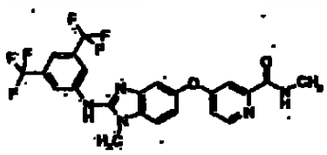
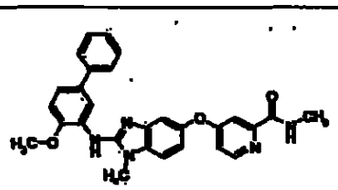
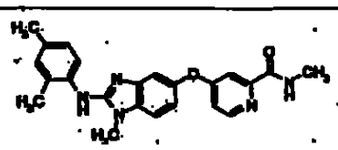
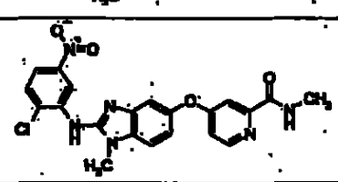
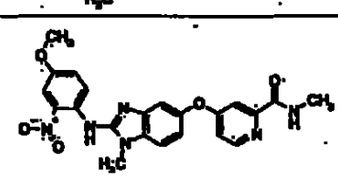
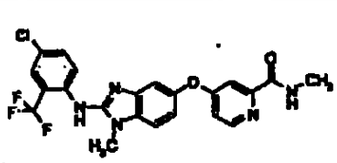
Ejemplo	Estructura	Nombre	MH+
132		N-metil[4-(1-metil-2-{[4-(metiletil) fenil]amino} bencimidazol-5-iloxi)(2-piridil)]carboxamida	416.3
133		(4-{2-[(3,4-diclorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	442.1
134		(4-{2-[(4-bromo-3-metil-fenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	466.1
135		(4-{2-[(3,4-dimetilfenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	402.2
136		(4-{2-[(3-cloro-4-fluoro-fenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	426.1
137		Metil-4-({1-metil-5-[2-(N-metilcarbamoil)(4-piridil-oxi)] bencimidazol-2-il}amino)-benzoato	432.2
138		(4-{2-[(4-bromo-3-cloro-fenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	486.0
139		(4-{2-[(3-bromofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metilcarboxamida	452.1
140		(4-{2-[(4-acetilfenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metilcarboxamida	416.2
141		[4-(2-{[4-(ter-butil)fenil]-amino}-1-metilbencimidazol-5-iloxi)(2-piridil)]-N-metil-carboxamida	430.2

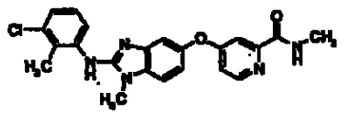
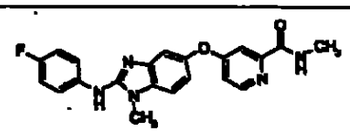
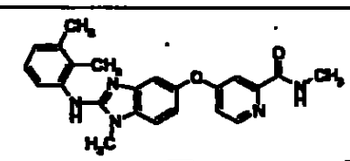
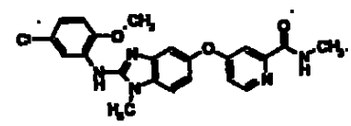
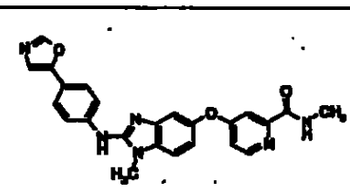
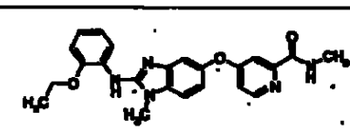
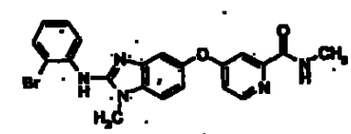
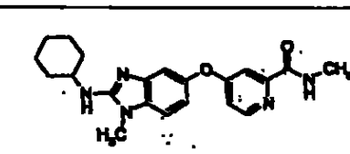
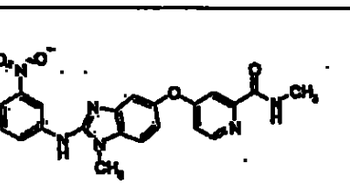
Ejemplo	Estructura	Nombre	MH+
142		(4-{2-[(4-metoxifenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	404.2
143		(4-{2-[(4-ciclohexilfenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	456.2
144		(4-{2-[(3,4-difluorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	410.2
145		(4-{2-[(4-metoxi-2-metil-fenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	418.2
146		(4-{2-[(3-clorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	408.1
147		(4-{2-[(3-fluorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	392.2
148		4-({1-metil-5-[2-(N-metil-carbamoil)(4-piridiloxi)]-bencimidazol-2-il}amino)-acido benzoico	418.2
149		N-metil{4-[1-metil-2-(fenilcarbonilamino)-bencimidazol-5-ilxi](2-piridil)}carboxamida	402.2
150		[4-(2-{[2-cloro-5-(trifluoro-metil)-amino}-1-metilbencimidazol-5-iloxi)(2-piridil)]-N-metil-carboxamida	476.1
151		(4-{2-[(2,5-dimetoxifenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	434.2

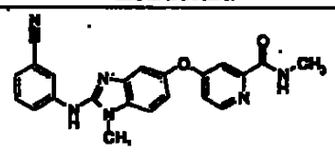
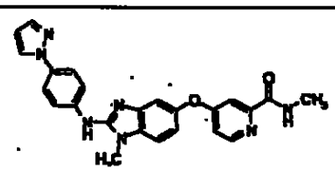
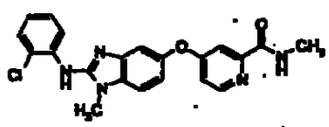
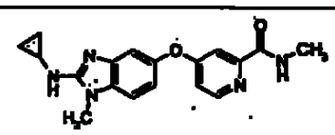
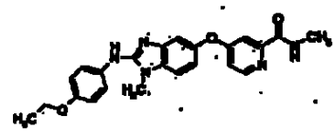
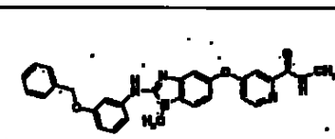
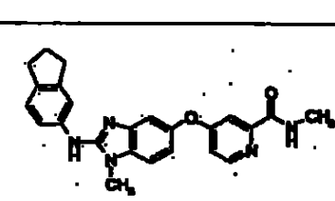
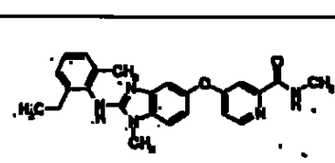
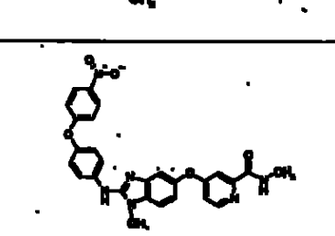
Ejemplo	Estructura	Nombre	MH+
152		(4-{2-[(2,4-difluorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	410.2
153		(4-{2-[(3,5-difluorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	410.2
154		(4-{2-[(4-etilfenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	402.2
155		(4-{2-[(4-clorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	408.2
156		(4-{2-[(4-bromo-3-metil-fenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	466.1
157		(4-{2-[(2-metoxi-4-nitro-fenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	448.4
158		N-metil[4-(1-metil-2-{[2-(trifluorometil)fenil]amino}bencimidazol-5-iloxi)(2-piridil)]-carboxamida	441.4
159		(4-{2-[(3-metoxifenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	403.4
160		(4-{2-[(2-etilfenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	401.4

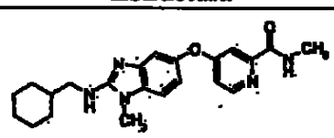
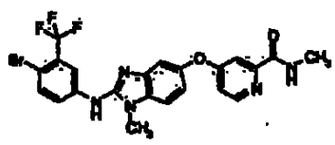
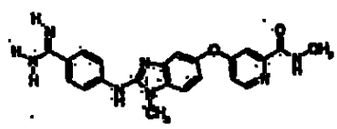
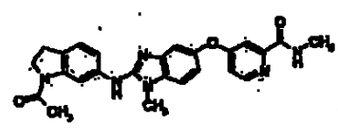
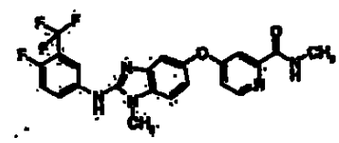
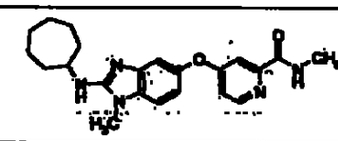
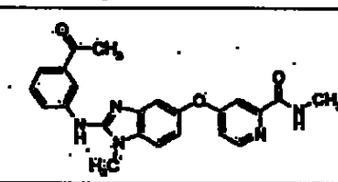
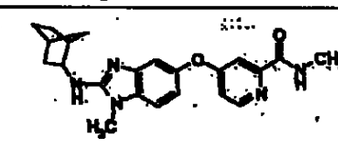
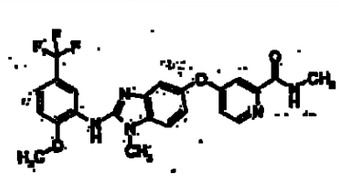
Ejemplo	Estructura	Nombre	MH+
161		(4-{2-[(2,5-difluorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	409.3
162		(4-{2-[(2,6-diclorofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	442.3
163		(4-{2-[(4-etilfenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	388.2
164		N-metil(4-{1-metil-2-[(2-metiltiofenil) amino]-bencimidazol-5-il-oxi}(2-piridil)) carboxamida	420.1
165		N-metil(4-{1-metil-2-[(4-metiltiofenil) amino]-bencimidazol-5-il-oxi}(2-piridil)) carboxamida	420.1
166		N-metil(4-{1-metil-2-[(2-(trifluoromeoxi) fenil]-amino}-bencimidazol-5-il-oxi}(2-piridil)) carboxamida	458.1
167		[4-(2-{[2-fluoro-5-(trifluoro-meti)fenil] amino}-1-metilbencimidazol-5-iloxi) (2-piridil)]-N-metilcarboxamida	460.1
168		(4-{2-[(4-cianofenil)amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	399.1
169		N-metil[4-(1-metil-2-{[3-(trifluorometil) fenil]amino}-bencimidazol-5-iloxi)(2-piridil)] carboxamida	442.1

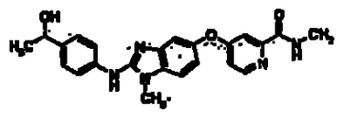
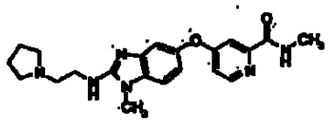
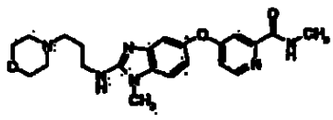
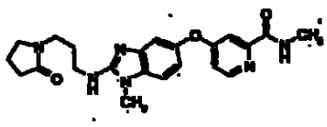
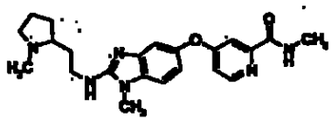
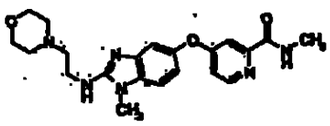
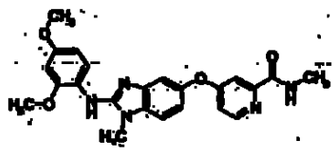
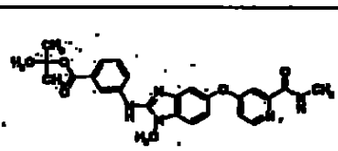
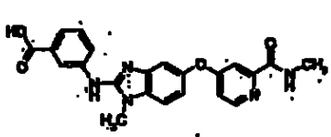
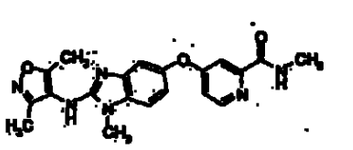
Ejemplo	Estructura	Nombre	MH+
170		N-metil[4-(1-metil-2-{[2-(metiletil) fenil]amino}-bencimidazol-5-iloxi)(2-piridil)] carboxamida	416.2
171		(4-{2-[(5-cloro-2,4-dimetoxi-fenil) amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	468.2
172		N-metil(4-{1-metil-2-[(2-fenilfenil) amino]bencimidazol-5-iloxi})2-piridil))-carboxamida	450.2
173		(4-{2-[(3-etilfenil) amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	402.2
174		(4-{2-[(3-fluorofenil) amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	392.1
175		(4-{2-[(4-bromofenil) amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	466.1
176		(4-{2-[(4-aminofenil) amino]-1-metilbencimidazol-5-il-oxi}(2-piridil))-N-metil-carboxamida	389.2
177 (síntesis como en ejemplo 1)		N-metil[4-(1-metil-2-{[4-(metilamino) fenil]amino}-bencimidazol-5-iloxi)(2-piridil)] carboxamida	403.2
178 (síntesis como en ejemplo 1)		[4-(2-{[4-(dimetilamino)-fenil]amino}-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-metilcarboxamida	417.2

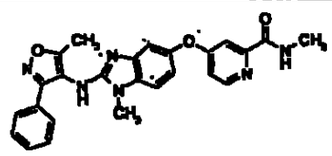
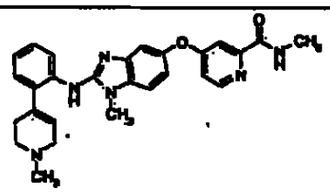
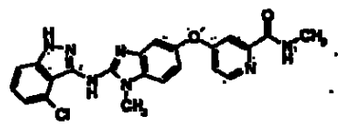
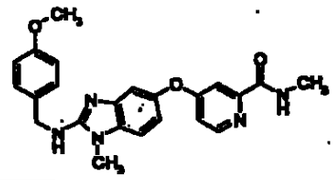
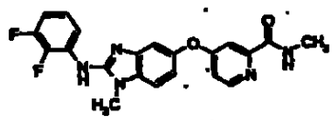
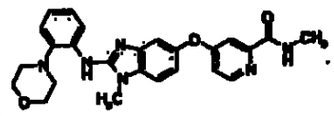
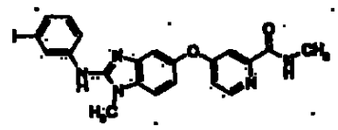
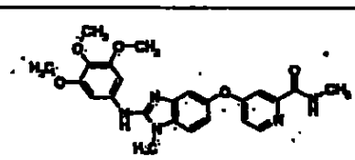
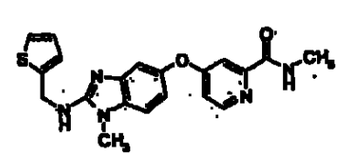
Ejemplo	Estructura	Nombre	MH+
179		N-metil-4-[(1-metil-2-{(5-metil-2-(metiloxi)fenil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-caboxamida	418.5
180		4-[(2-{[3,5-Bis(metiloxi)-fenil]amino} –1-metil-1H-bencimidazol-5-il)oxi]-N – metilpiridin-2-carboxamida	434.5
181		4-({2-[(2,6-difluorofenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpirirdin-2-carboxamida	410.4
182		4-[(2-{[3,5-Bis(trifluorometil)-fenil]amino} –1-metil-1H-bencimidazol-5-il)oxi]-N – metilpiridin-2-carboxamida	510.4
183		N-metil-4-[(1-metil-2-{(4-(metiloxi) –1, 1'-bifenil-3-il]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-caboxamida	480.5
184		4-({2-[(2,4-dimetilfenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpirirdin-2-carboxamida	480.5
185		4-({2-[(2-cloro-5-nitrofenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpirirdin-2-carboxamida	453.9
186		N-metil-4-[(1-metil-2-{(4-(metiloxi) –2-nitrofenil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-caboxamida	449.4
187		4-[(2-{[4-cloro-2-(trifluoro-metil) fenil]amino]-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	476.9

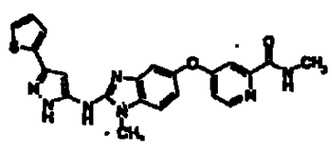
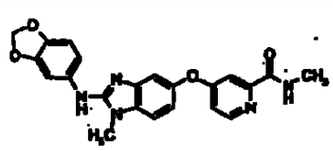
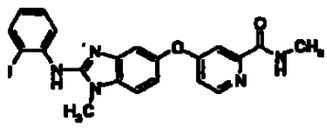
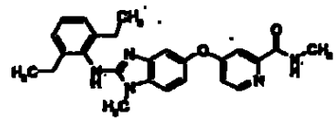
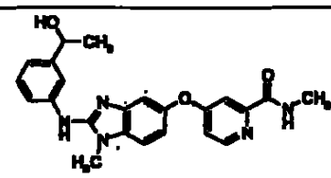
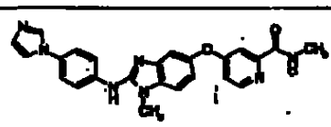
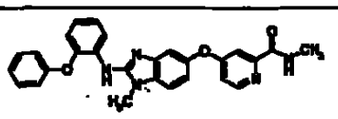
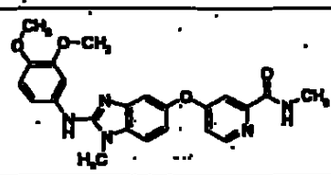
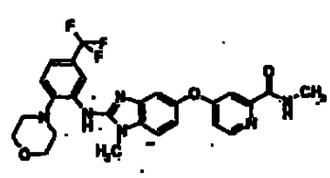
Ejemplo	Estructura	Nombre	MH+
188		4-({2-[(3-cloro-2-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	422.9
189		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	392.4
190		4-({2-[(2,3-dimetilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	402.5
191		4-[(2-{[5-cloro-2-(metiloxi) fenil] amino]-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	438.9
192		N-metil-4-[(1-metil-2-{[4-(1,3-oxazol-5-il) fenil] aino}-1H-bencimidazol-5-il)oxi]- piridin-2-caboxamida	441.5
193		4-[(2-{[2-(etiloxi) fenil] amino]-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	418.5
194		4-({2-[(2- bromofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	453.3
195		4-{[2-(ciclohexilamino)-1-metil-1H-bencimidazol-5-il]-oxi)-N-metilpiridin-2-carboxamida	380.5
196		N-metil-4-({1-metil-2-[(3-nitrofenil) amino]-1H-bencimidazol-5-il}oxi) piridin-2-carboxamida	419.4

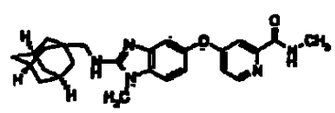
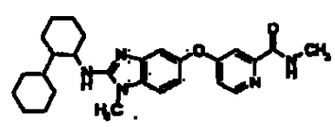
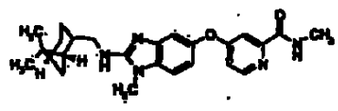
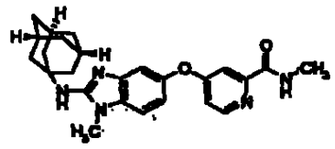
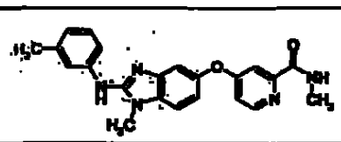
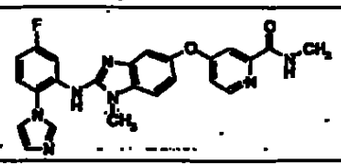
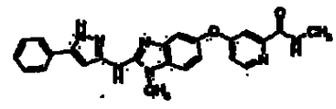
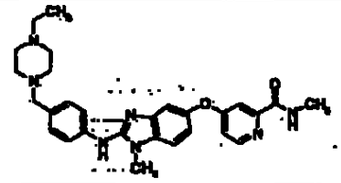
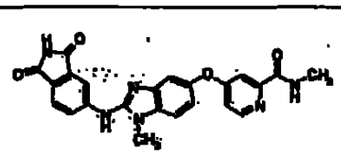
Ejemplo	Estructura	Nombre	MH+
197		4-({2-[(3-cianofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	399.4
198		N-metil-4-[(1-metil-2-{[4-(1H-pirazol-1- il) fenil]-amino}-1H-bencimidazol-5-il)-oxi] piridin-2-carboxamida	440.5
199		4-({2-[(2-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	408.9
200		4-{[2-(ciclopropilamino)-1-metil-1H-bencimidazol-5-il]-oxi)-N-metilpiridin-2-carboxamida	338.4
201		4-[(2-{[4-(etiloxil) fenil] amino]-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	418.5
202		N-metil-4-{[1-metil-2-({3-[(fenilmetil) oxi]fenil}amino)-1H-bencimidazol-5-il]oxi}-piridin-2-carboxamida	480.5
203		4-{[2-(2,3-dihidro-1H-inden-5-ilamino)-1-metil-1H-bencimidazol-5-il]-oxi)-N-metilpiridin-2-carboxamida	414.5
204		4-({2-[(2-etil-6-metilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	416.5
205		N-metil-4-{[1-metil-2-({4-[(4-nitrofenil) oxi]fenil}- amino)-1H-bencimidazol-5-il]oxi}-piridin-2-carboxamida	511.5

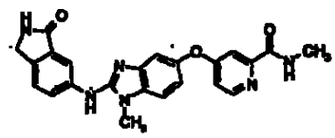
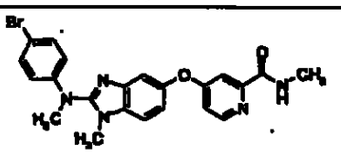
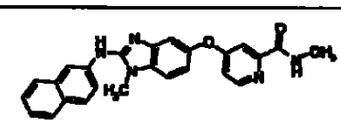
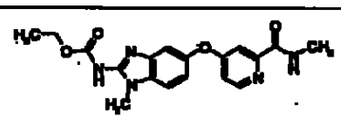
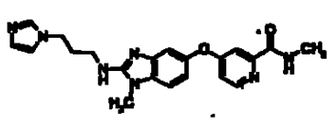
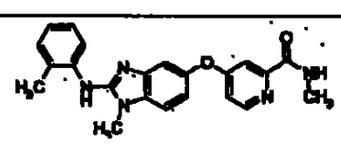
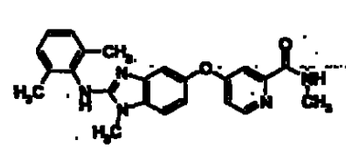
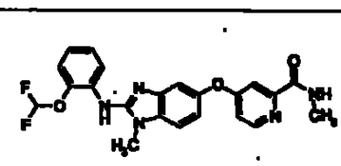
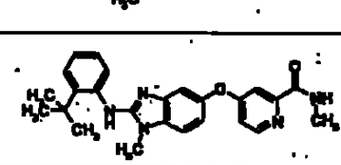
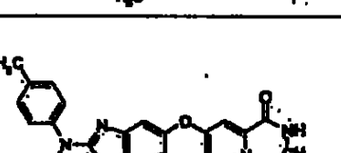
Ejemplo	Estructura	Nombre	MH+
206		4-({2-[(ciclohexilmetil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	394.5
207		4-[(2-{[4-bromo-3-(trifluoro-metil) fenil] amino}-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	521.3
208		4-{[2-({4-[(Z)-amino(imino)-metil]fenil}amino)-1-metil-1H-bencimidazol-5-il]-oxi)-N-metilpiridin-2-carboxamida	416.5
209		4-{[2-({4-[(Z)-amino(imino)-metil] fenil}amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	457.5
210		4-[(2-{[4-fluoro-3-(trifluorometil) fenol]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	460.4
211		4-{[2-(cicloheptilamino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpridini-2-carboxamida	394.5
212		4-({2-[3-acetilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	416.5
213		4-{[2-(biciclo[2,2,1)hep-2-ilamino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metil-piridin-2-carboxamida	392-5
214		N-metil-4-[(1-metil-2-{[2-(metiloxi)-5-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	472.4

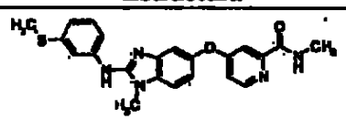
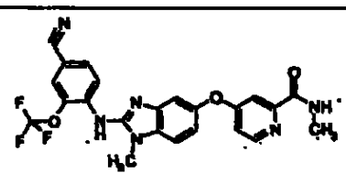
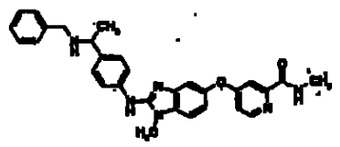
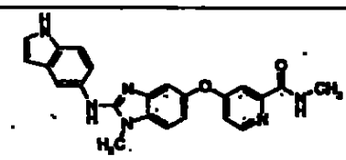
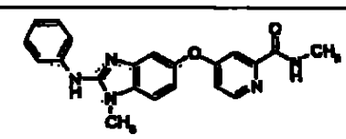
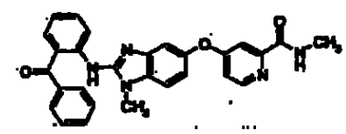
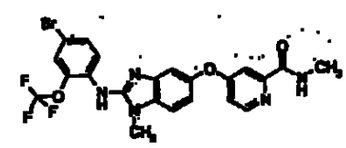
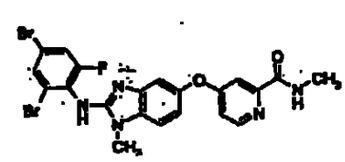
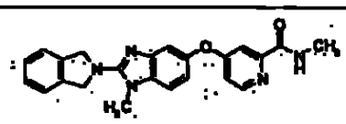
Ejemplo	Estructura	Nombre	MH+
215		4-[(2-{[4-(1-hidroxietil)-fenil] amino}-1-metil -1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	418.5
216		N-metil-4-({1-metil-2{(2-pirolidin-1-iletil)amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	395.5
217		N-metil-4-({1-metil-2-[(3-morfolin-4-ilpropil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	425.5
218		N-metil-4-[(1-metil-2-{[3-(2-oxipirolidin)-1-il)propil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	423.5
219		N-metil-4-[(1-metil-2-{[2-(1-metilpirolidin)-2-il)etil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	409.5
220		N-metil-4-({1-metil-2-[(2-morfolin-4-iletil)amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	411.5
221		4-[(2-{[2,4-Bis(metiloxi)-fenil] amino} -1-metil -1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	434.5
222		1,1-dimetiletil-3-{[1-metil-5-({2-[(metilamino)carbonil]-piridin-4-il} oxi)-1H-bencimidazol-2-il] amino} benzoato	474.5
223		3-{[1-metil-5-({2-[(metil-amino) carbonil]piridin-4-il}-oxi)-1H-bencimidazol-2-il]-amino}acido benzoico	418.4
224		4-({2-[(3,5-dimetilsoxazol-4-il)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	393.4

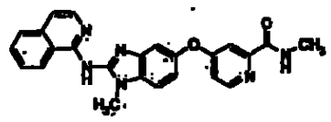
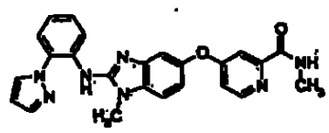
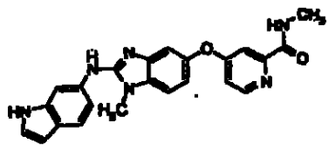
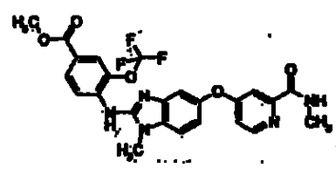
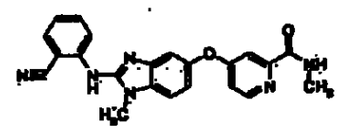
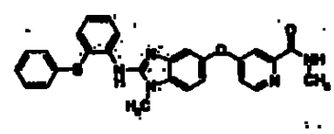
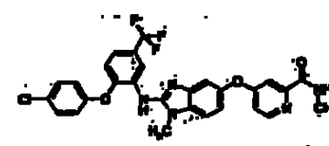
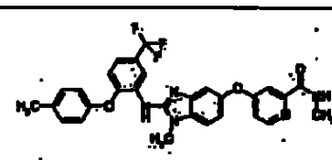
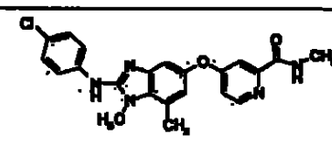
Ejemplo	Estructura	Nombre	MH+
225		N-metil-4-({1-metil-2-[(5-metil-3-fenilsoxazol-4-il)- amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	455.5
226		N-metil-4-[(1-metil-2-{[2-(1-metil-1,2,3,6,-tetrahidro-piridin-4-il)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	469.6
227		4-({2-[(4-cloro-1H-indazol-3-il)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	448.9
228		N-metil-4-{[1-metil-2-({[4-(metiloxi)fenil]metil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	418.5
229		4-({2-[(2,3-difluorofenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	410.4
230		N-metil-4-({1-metil-2-[(2-morfolin-4-ilfenil)- amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	459.5
231		4-({2-[(3-iodofenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	500.3
232		N-metil-4-[(1-metil-2-{[3,4,5-tris(metiloxi)fenil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	464.5
233		N-metil-4-({1-metil-2-[(tien-2-ilmetil)- amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	394.5

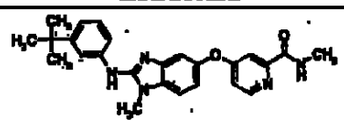
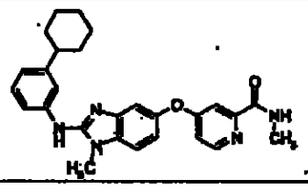
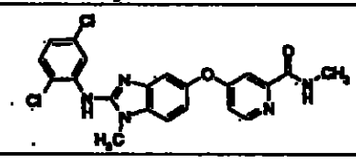
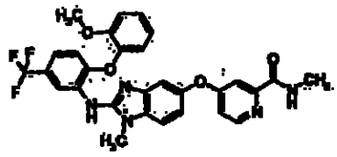
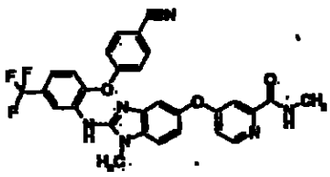
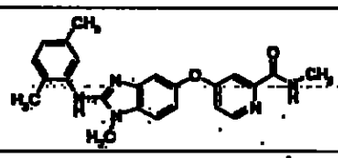
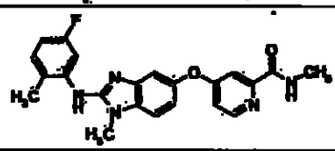
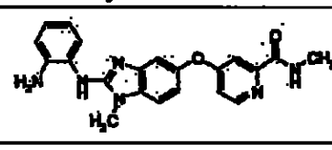
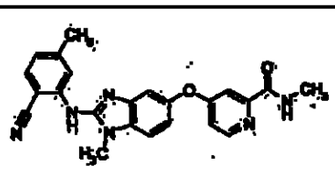
Ejemplo	Estructura	Nombre	MH+
234		N-metil-4-({1-metil-2-[(3-tien-2-il-1H-pirazol-5-il)- amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	446.5
235		4-{[2-(1,3-benzodioxol-1-il-amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	418.4
236		4-({2-[(2-iodofenil)-amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	500.3
237		4-({2-[(2,6-dietilfenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	430.5
238		4-[(2-{[3-(1-hidroxietil)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	418.5
239		4-[(2-{[4-(1H-imidazol-1-il)-fenil-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	440.5
240		N-metil-4-[(1-metil-2-{[2-(feniloxi) fenil]-amino}-1H-bencimidazol-5-il)oxi] piridin-2-carboxamida	466.5
241		4-[(2-{[3,4-Bis(metiloxi)-fenil-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	434.5
242		N-metil-4-[(1-metil-2-{[2-morfolin-4-il-5-(trifluoro-metil) fenil]-amino}-1H-bencimidazol-5-il)oxi] piridin-2-carboxamida	527.5

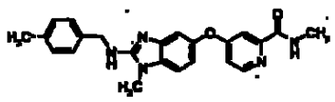
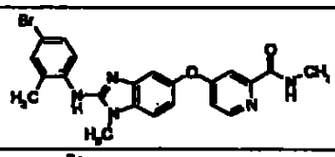
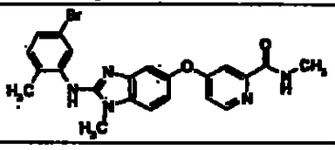
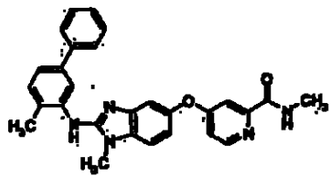
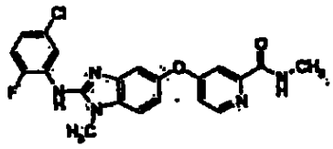
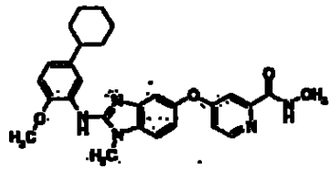
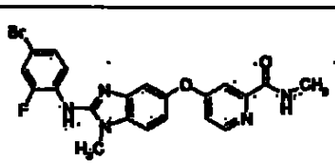
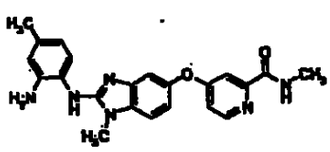
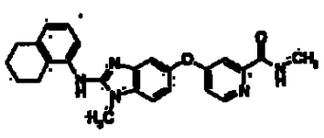
Ejemplo	Estructura	Nombre	MH+
243		N-metil-4-({1-metil-2-[(triciclo[3.3.1~3,7~]dec-1-ilmetil)amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	446.6
244		4-({2-[1,1'-Bi(ciclohexil)--ilamino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	462.6
245		4-{[2-({[(1S,5,S)-6,6-dimetil-biciclo [3.1.1]peto-2-il]metil}-amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	434.6
246		N-metil-4-{[1-metil-2-(triciclo[3.3.1.1~3,7~]dec-1-ilamino-1H-bencimidazol-5-il]-oxi}-piridin-2-carboxamida	432.5
247		N-metil-4-({1-metil-2-[(3-metilfenil)-amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	388.4
248		4-[(2-{[5-fluoro-2-(1H-imidazol-1-il) fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	458.5
249		N-metil-4-({1-metil-2-[(5-fenil-1H-pirazol-3-il)amino]-1H-. bencimidazol-5-il}-oxi)-piridin-2-carboxamida	440.5
250		4-{[2-({4-[(4-etilpiperazin)-1-il)metil]fenil}amino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin -2-carboxamida	500.6
251		4-({2-[(1,3-dioxo-2,3-dihidro-1H-isoindol-5-il)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	443.4

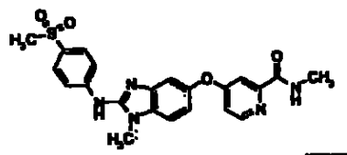
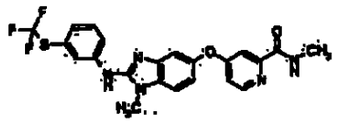
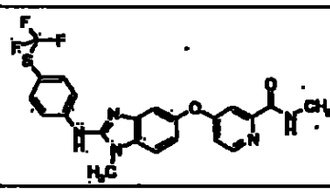
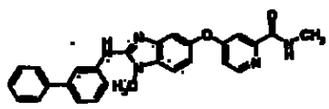
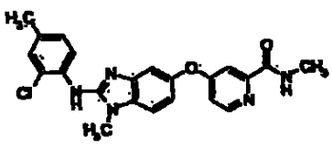
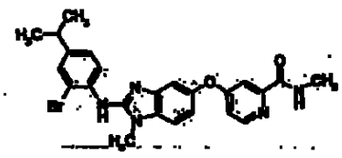
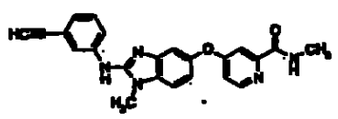
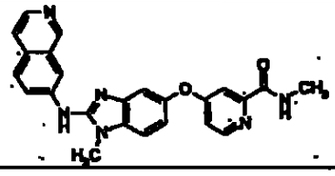
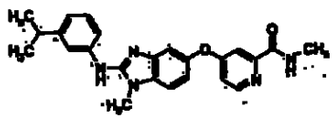
Ejemplo	Estructura	Nombre	MH+
252		N-metil-4-({1-metil-2-[(3-oxo-2,3-dihidro-1H-isoindol-5-il)amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	429.4
253		4-({2-[(4-bromofenil)-(metil)amino-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	467.3
254		N-metil-4-{[1-metil-2-(naftalen-2-il-amino)-1H-bencimidazol-5-il]-oxi}-piridin-2-carboxamida	424.5
255		Etil-1-metil-5-({2-[(metil-amino) carbonil]piridin-4-il}-oxi)-1H-bencimidazol-2-il-carbamato	370.4
256		4-[(2-{[3-(1H-imidazol-1-il) – propil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	406.5
257		N-metil-4-({1-metil-2-[2-metilfenil) amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	388.4
258		4-({2-[(2,6-dimetilfenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	402.5
259		4-{[2-({2-[(difluorometil)-oxi]fenil} amino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin -2-carboxamida	440.4
260		4-[(2-{[2-(1,1-dimetiletil) –fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	430.5
261		N-metil-4-({1-metil-2-[metil(4-metilfenil) amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	402.5

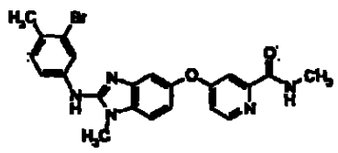
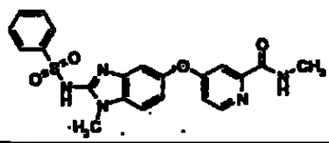
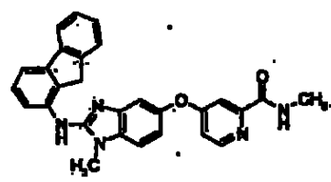
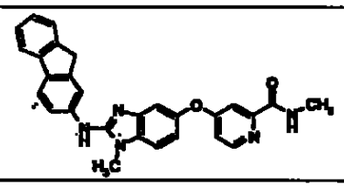
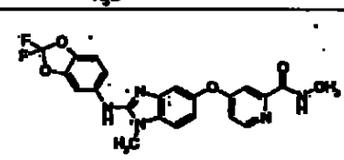
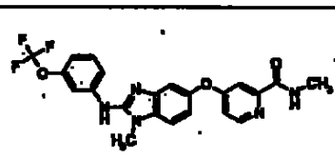
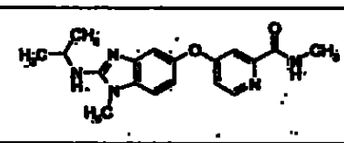
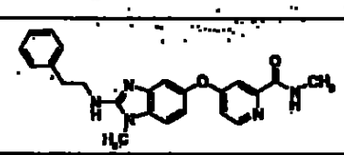
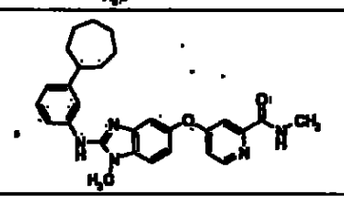
Ejemplo	Estructura	Nombre	MH+
262		N-metil-4-[(-1-metil-2-{[3-(metilito) fenil]amino}-1H-bencimidazol-5-il) oxi]piridin-2-carboxamida	483.4
263		4-{[2-({4-ciano-2-[]trifluoro-metil) oxi]fenil}amino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin -2-carboxamida	483.4
264		N-metil-4-({1-metil-2-[(4-{1-[(fenilmetil)amino]-etil}fenil)amino]-1H-bencimidazol-5-il}-oxi)-piridin-2-carboxamida	507.6
265		4-{[2-(1H-indol-5-ilamino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin -2-carboxamida	413.5
266		N-metil-4-{[1-metil-2-(fenilamino)-1H-bencimidazol-5-il] oxi}piridin-2-carboxamida	374.4
267		N-metil-4-[(1-metil-2-{[2-(fenilcarbonil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	478.5
268		4-{[2-({4-bromo-2-[trifluorometil] oxi}fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi}-N-metilpridin-2-carboxamida	537.3
269		4-{[2-[{2,4-dibromo-6-fluorofenil} amino]-1-metil-1H-bencimidazol-5-il]oxi}-N-metilperidin-2-carboxamida	550.2
270		4-{[2-(1,3-dihidro-2-h-isoindol-2-il)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	400.5

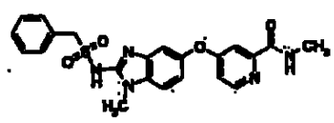
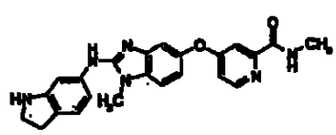
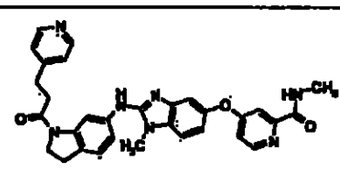
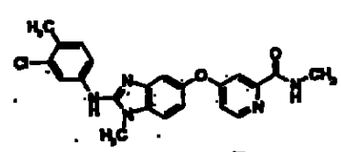
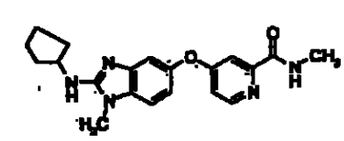
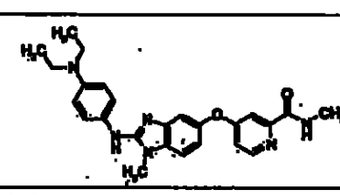
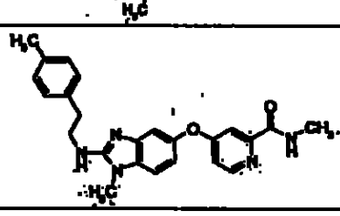
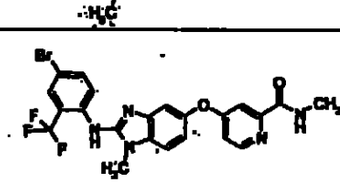
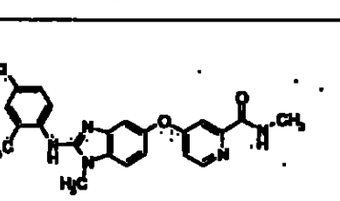
Ejemplo	Estructura	Nombre	MH+
271		4-{[2-(isoquinolin-1-ilamino)-1-metil-1H-bencimidazol-5-il-oxi]-N-metilpiridin-2-carboxamida	425.5
272		N-metil-4-[(1-metil-2-{[2-(1H-pirazol-1-il)fenil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	440.5
273		4-{[2-(1H-indol-6-ilamino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin-2-carboxamida	413.5
274		Metil-4-{[1-metil-5-({2-[(metilamino) carbonil]piridin-4-il}oxi-1H-bencimidazol-2-il)amino]-3-[(trifluorometil)-oxi]benzoato	516.4
275		4-({2[(2-cianofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	399.4
276		N-metil-4-[(1-metil-2-{[2-(feniltio) fenil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	482.6
277		4-[(2-{[2-[(4-clorofenil)oxi[-5-(trifluorometil)fenil]-amino]-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	569.0
278		N-metil-4-[(1-metil-2-{[2-[(4-metilfenil oxi]-5-(trifluorometil) fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	548.5
279		4-({2[(4-clorofenil)amino]-1,7-dimetil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	422.9

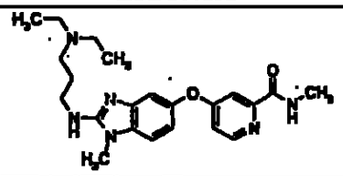
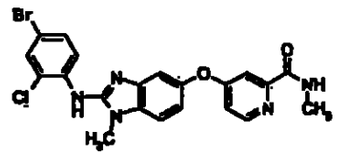
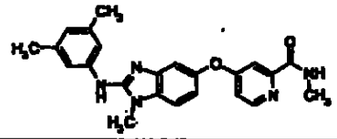
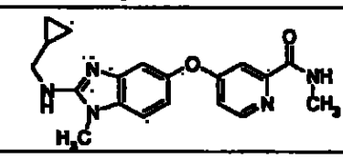
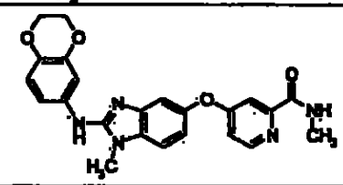
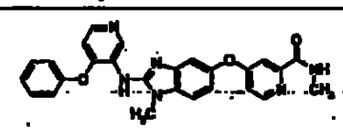
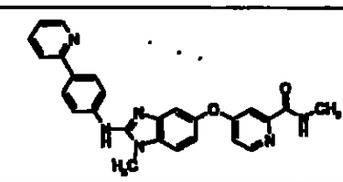
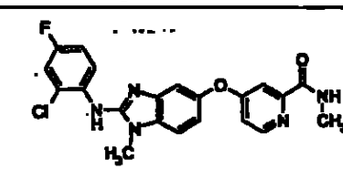
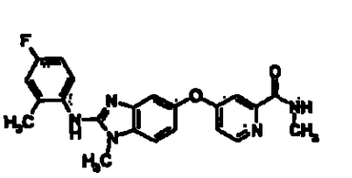
Ejemplo	Estructura	Nombre	MH+
280		4-[(2-{[3-(1,1-dimetil)-fenil]amino-1H -bencimidazol-5-il]oxi}-N-metilpiridin -2-carboxamida	430.5
281		4-({2-[(3-ciclohexilfenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	456.6
282		4-({2-[(2,5-diclorofenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)->N-metilpiridin-2-carboxamida	443.3
283		N-metil-4-[(1-metil-2-{[2-{[2-(metiloxi) fenil]oxi}-5-(trifluorometil) fenil]amino}-1H-bencimidazol-5-il) oxi]piridin-2-carboxamida	564.5
284		4-[(2-{[2-[(4-cianofenil)oxi]-5-(trifluorometil)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi].N-metilpiridin-2-carboxamida	559.5
285		4-({2-[(2,5-dimetilfenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	402.5
286		4-({2-[(5-fluoro-2-metil-fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	406.4
287		4-({2-[(2-aminofenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	389.4
288		4-({2-[(2-ciano-5-metil-fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)->N-metilpiridin-2-carboxamida	413.5

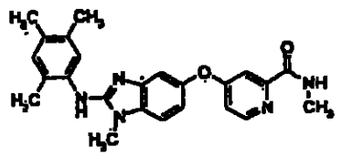
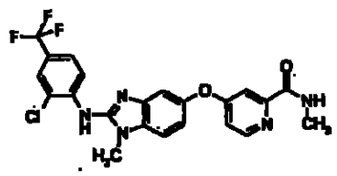
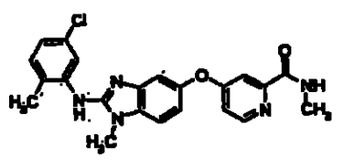
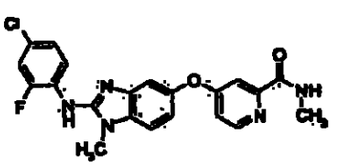
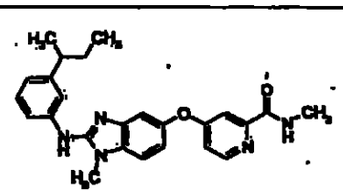
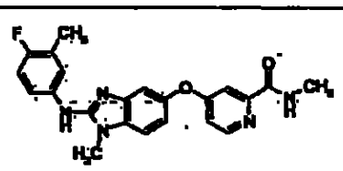
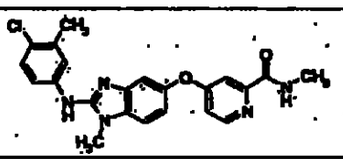
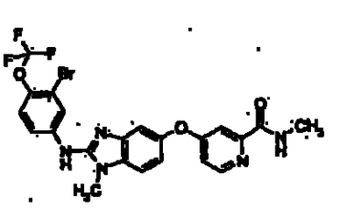
Ejemplo	Estructura	Nombre	MH+
289		N-metil-4-[(1-metil-2-{[(4-metilfenil)metil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	402.5
290		4-({2-[(4-bromo-2-metil-fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	467.3
291		4-({2-[(5-bromo-2-metil-fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	467.3
292		N-metil-4-({1-matil-2-[(4-metil-1,1' bifenil-3-il)-amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	464.5
293		4-({2-[(5-cloro-2-fluoro-fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	426.8
294		4-[(2-{[2-{[5-coclihexil-2-(metil-oxi)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi].N-metilpiridin-2-carboxamida	486.6
295		4-({2-[(4-bromo-2-fluoro-fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	471.3
296		4-({2-[(2-amino-4-metil-fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	403.5
297		N-metil-4-{[1-metil-2-(5,6,7,8,-tetrahidronaftalen-1-ilamino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	428.5

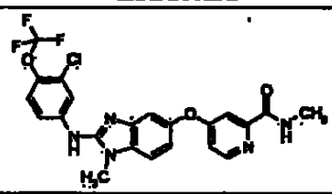
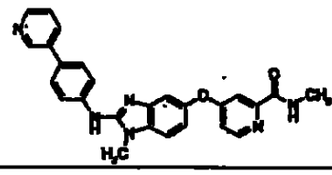
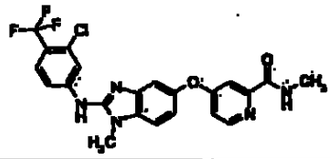
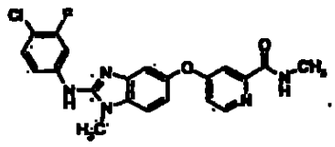
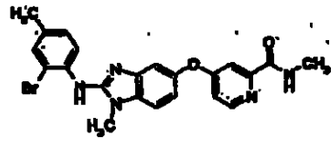
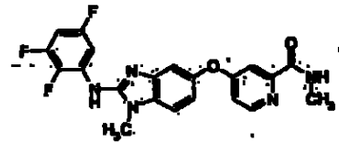
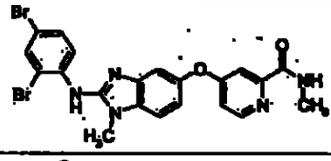
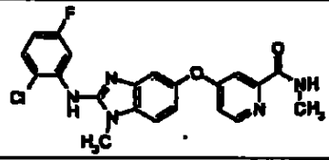
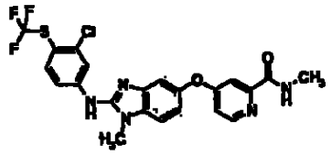
Ejemplo	Estructura	Nombre	MH+
298		N-metil-4-[(1-metil-2-{[4-(metilsulfonil)fenil]amino}-1-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	452.5
299		N-metil-4-{[1-metil-2-({3-[(trifluorometil)tio]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	474.5
300		N-metil-4-{[1-metil-2-({4-[(trifluorometil)tio]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	474.5
301		4-{[2-(1,1'-bifenil-3-ilamino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	450.5
302		4-({2-[(2-cloro-4-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	422.9
303		4-[(2-{[2-bromo-4-(1-metiletil) fenil]amino}-1-metil-1H-bencimidazol -5-i)oxi]-N-metilpiridin-2-carboxamida	495.4
304		4-{[2-(3-etinilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	398.4
305		4-{[2-(isoquinolin-7-ilamino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	425.5
306		N-metil-4-[(1-metil-2-{[3-(1-metiletil) fenil]amino}-1-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	416.5

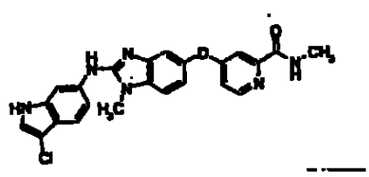
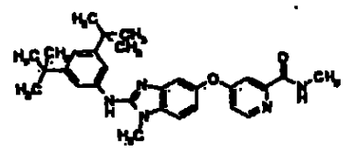
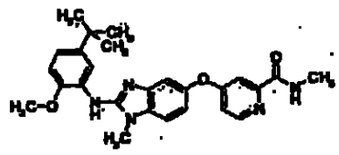
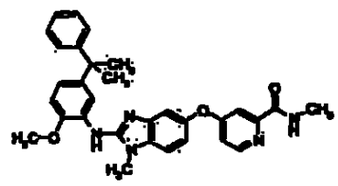
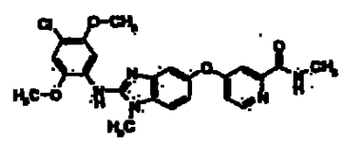
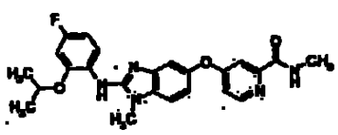
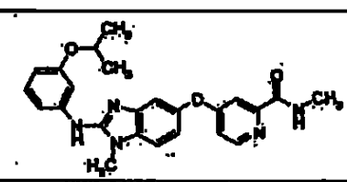
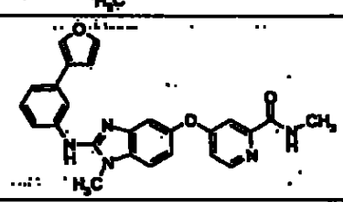
Ejemplo	Estructura	Nombre	MH+
307		4-({2-[(3-bromo-4-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	467.3
308		N-metil-4-({1-metil-2-[(fenilsulfonil) amino]- 1H-bencimidazol-5-il} oxi) piridin-2-carboxamida	438.5
309		4-{[2-(9H-fluoren-1-ilamino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	462.5
310		4-{[2-(9H-fluoren-2-ilamino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	462.5
311		4-({2-[(2,2-difluoro-1,3-benzodioxol-5-il)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	454.4
312		N-metil-4-{[1-metil-2-({3-[(trifluorometil)oxi]fenil} amino)-1H-bencimidazol-5-il] oxi} piridin-2-carboxamida	458.4
313		N-metil-4-({1-metil-2-[(1-metiletil) amino]- 1H-bencimidazol-5-il} oxi) piridin-2-carboxamida	340.4
314		N-metil-4-({1-metil-2-[(2-feniletil) amino]- 1H-bencimidazol-5-il} oxi) piridin-2-carboxamida	402.5
315		4-({2-[(3-cicloheptilfenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	470.6

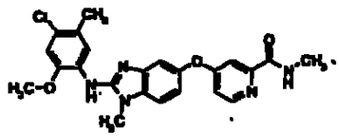
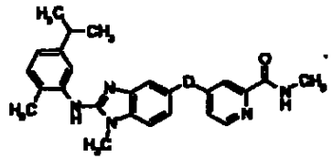
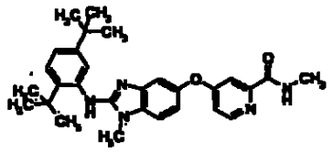
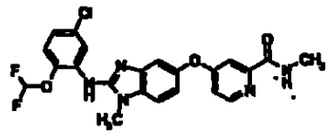
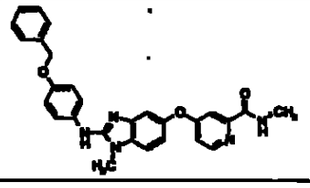
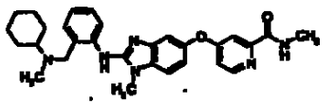
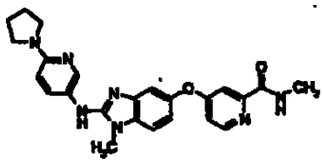
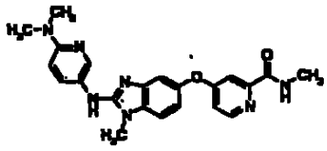
Ejemplo	Estructura	Nombre	MH+
316		N-metil-4-[(1-metil-2-{[(fenilmetil) sulfonil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	452.5
317		4-{[2-(2,3-dihidro-1H-indol-6-ilamino) -1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	415.5
318		N-metil-4-[(1-metil-2-{[1-(3-piridin-4-ilpropanoil)-2,3-dihidro-1H-indol-6-il]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	548.6
319		4-({2-[(3-cloro-4-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	422.9
320		4-{[2-(ciclopentilamino) -1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	321
321 (síntesis como en ejemplo 1)		4-[(2-{[4-(dietilamino)fenil]-amino} -1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	445.5
322		N-metil-4-[(1-metil-2-{[2-(4-metilfenil)etil] amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	416.5
323		4-[(2-{[4-bromo-2-(trifluorometil) fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	521.3
324		4-({2-[(4-cloro-2-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	422.9

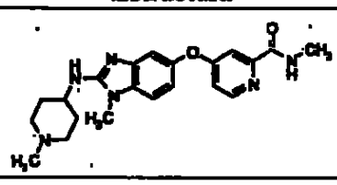
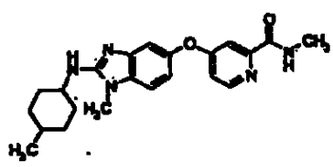
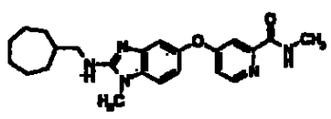
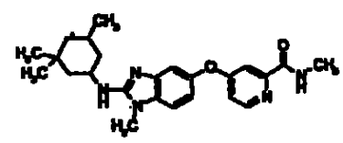
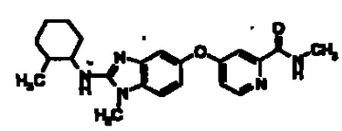
Ejemplo	Estructura	Nombre	MH+
325		4-[(2-{[3-(dietilamino)propil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	411.5
326		4-({2-[(4-bromo-2-cloro-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	487.8
327		4-({2-[(3,5-dimetilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	402.5
328		4-({2-[(ciclopropilmetil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	352.4
329		4-{[2-(2,3-dihidro-1,4-benzodioxin-6-ilamino-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	432.4
330		N-metil-4-[(1-metil-2-{[4-(feniloxi) piridin-3-il]-amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	467.5
331		N-metil-4-({1-metil-2-[(4-piridin-2-ilfenil]amino)-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	451.5
332		4-({2-[(2-cloro-4-fluoro-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	426.8
333		4-({2-[(4-fluoro-2-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	406.4

Ejemplo	Estructura	Nombre	MH+
334		N-metil-4-({1-metil-2-[(2,4,5-trimetilfenil)amino]-1H-bencimidazol-5-il}oxi).piridin-2-carboxamida	416.5
335		4-[(2-{[2-cloro-4-(trifluoro-metil)fenil] amino}-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	476.9
336		4-({2-[(5-cloro-2-metil-fenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	422.9
337		4-({2-[(4-cloro-2-fluoro-fenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	426.8
338		N-metil-4-[(1-metil-2-{[3-(1-metilpropil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	430.5
339		4-({2-[(4-fluoro-3-metil-fenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	406.4
340		4-({2-[(4-cloro-3-metil-fenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	422.9
341		4-{[2-({3-bromo-4-[(trifluoro-metil)oxi]fenil} amino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin-2-carboxamida	537.3

Ejemplo	Estructura	Nombre	MH+
342		4-{[2-({3-cloro-4-[(trifluoro-metil)oxi]fenil} amino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin-2-carboxamida	492.9
343		N-metil-4-({1-metil-2-[(4-piridin-3-ilfenil)amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	451.5
344		4-[(2-{[3-cloro-4-(trifluoro-metil)fenil] amino}-1-metil-1H-bencimidazol-5-il)-oxi]-N-metilpiridin-2-carboxamida	476.9
345		4-({2-[(4-cloro-3-fluoro-fenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	426.8
346		4-({2-[(2-bromo-4-metil-fenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	467.3
347		N-metil-4-({1-metil-2-[(2,3,5-trifluorofenil) amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	428.4
348		4-({2-[(2,4-dibromofenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	532.2
349		4-({2-[(2-cloro-5-fluoro-fenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	426.8
350		4-{[2-({3-cloro-4-[(trifluoro-metil) tio]fenil} amino)-1-metil-1H-bencimidazol-5-il]-oxi}-N-metilpiridin-2-carboxamida	508.9

Ejemplo	Estructura	Nombre	MH+
351		4-({2-[(3-cloro-1H-indol-6-il) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	447.9
352		4-[(2-{[3,5-Bis(1,1-dimetil-etil) fenil]amino}-1-metil-1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	486.6
353		4-[(2-{[5- (1,1-dimetil-etil)-2-(metiloxi)fenil] amino}-1-metil-1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	460.5
354		N-metil-4-[(1-metil-2-{[2-(metiloxi)-5-(1-metil-1-feniletil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	522.6
355		4-[(2-{[4.cloro-2,5-Bis(metiloxi)fenil] amino}-1-metil-1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	468.9
356		4-{[2-({4-fluoro-2-[(1-metil-etil)oxi]fenil}amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	450.5
357		N-metil-4-{[1-metil-2-({3-[(1-metiletil)oxi]fenil}-amino)-1H-bencimidazol-5-il]-oxi}piridin-2-carboxamida	432.5
358 (síntesis como en ejemplo 769)		4-({2-[(3-furan-3-ilfenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	440.5

Ejemplo	Estructura	Nombre	MH+
359		4-[(2-{[4-cloro-5-metil-2-(metiloxi)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboximamida	452.9
360		N-metil-4-[(1-metil-2-{[2-metil-5-(1-metiletil)fenil]amino}-1H-bencimidazol-5-il)-oxi]piridin-2-carboxamida	430.5
361		4-[(2-{[2,5-bis(1,1-dimetil-etil)-2-(metiloxi)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	486.6
362		4-{[2-({5-cloro-2-[(difluorometil)oxi]fenil}amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	474.9
363		N-metil-4-{[1-metil-2-({4-[(fenilmetil)oxi]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	480.5
364		4-({2-[(2-{[ciclonexil](metil)-amino}metil)fenil]amino}-1-metil-1H-bencimidazol-5-il)-oxi)-N-metilpiridin-2-carboxamida	499.6
365		N-metil-4-({1-metil-2-[(6-pirrolidin-1-ilpiridin-3-il)-amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	444.5
366		4-[(2-{[6-(dimetilamino)-piridin-3-il]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboximamida	418.4

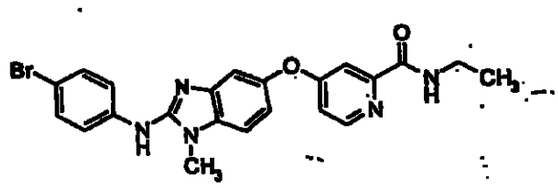
Ejemplo	Estructura	Nombre	MH+
367		N-metil-4-({1-metil-2-[(1-metilpiperidin-4-il)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	395.4
368		N-metil-4-({1-metil-2-[(4-metilciclohexil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	394.4
369		4-({2-[(cicloheptilmetil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	408.5
370		N-metil-4-({1-metil-2-[(3,3,5--trimetilciclohexil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	422.5
371		N-metil-4-({1-metil-2-[(2-metilciclohexil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	394.4

Ejemplo 372

Síntesis de 4-({2-[(4-bromofenil)amino}]-1-metil-

1H-bencimidazol-5-il}oxi)-N-etilpiridine-2-carboxamida

El compuesto 4-({2 [(4-bromofenil)amino]-1 metil-1H-benzimidazol-5-y1}oxy-N. etilpiridin-2-carboxamida fue Sintetizado como sigue:



Paso 1: Síntesis de terbutil-4-cloripiridina-2-carboxilato:

4-cloropiridina-2-carbonil (1eq) fue suspendido en tetrahidrofurano anhidro. Luego 2 equivalentes de una solución 1M de tert-butóxido de potasio fue añadida a cuenta gotas a la reacción lentamente agitando bajo nitrógeno. Después de 3 a 4 horas o cuando la reacción estuvo terminada determinada por el HPLC, la reacción fue evaporada bajo presión reducida y diluida con acetato de etilo. La capa orgánica fue lavada con agua y salmuera y luego secada sobre sulfato de sodio anhidro. Los extractos orgánicos fueron evaporados bajo presión reducida para dar el éster de terbutilo como un aceite amarillo. MS: MH+=214.

Paso 2: Síntesis de terbutil 4-(4amino-3-nitrofenoxi)piridin-2-carboxilate.

Un polvo sólido blanco anhidro pulverizado KHMDS (2 eq) fue suspendido en una solución de dimetil formamida. 4-amino-3-nitrofenol cristalino rojo (1eq) fue agregado a la solución agitando rápidamente bajo una atmósfera inerte y la solución heterogénea fue agitada por dos horas. Luego una solución de dimetilformamida con terbutil 4-cloro piridina 2 carboxilato 1 (eq) fue añadida a cuenta gotas. Carbonato de potasio anhidro pulverizado fue cargado a la reacción como un ácido limpiador "scavenger". La mezcla viscosa de color púrpura fue calentada a 80° por 12 a 15 horas hasta que se determinó por el TLCque estaba completa. La reacción fue evaporada bajo presión reducida y diluida con acetato de etilo en exceso y agua. Una extracción de la capa acuosa fue hecha con etil acetato. Las capas orgánicas fueron combinadas y lavadas 4 veces con agua seguida de salmuera. La capa orgánica fue secada sobre sulfato de sodio anhidro y evaporada bajo presión reducida. El

material crudo fue purificado por cromatogRafía "flash" de cíclica gel usando como eluente una mezcla de 1:1 de hexanos a etil acetato para dar el producto deseado. MSD: MH+=332.

Paso 3: Síntesis de ter-butil. 4-[3-nitro-4-(2,2,2,-trifluoroacetylamino) phenoxi] piridine-2. carboxilato:

Trifluroacético anhídro (1eq) fue lentamente añadido a cuenta gotas a una solución de la amina de arriba en cloruro de metileno anhidro bajo nitrógeno. Después de 10 a 15 minutos o hasta que la reacción se completa por determinación en el HPLC, la reacción fue apagada con exceso de bicarbonato de sodio acuoso saturado. El producto fue extractado con cloruro de metileno de la capa acuosa y lavado con agua y salmuera. Los extractos fueron secados sobre sulfato de sodio anhidro y evaporados bajo presión reducida para refinar el producto de ter-butil. 4-[3-nitro-4-(2,2,2,-trifluoroacetylamino) phenoxi] piridine-2. carboxilato como un sólido amarillo MS: MH+ = 428.

Paso 4: Síntesis de terbutil-4-[3nitro-4-(2,2,2-trifluoro-N-methylacetilamino) fenoxy] -piridin-2-carboxilate:

Una solución de terbutil 4-[3-nitro-4-(2,2,2-trifluoroacetilamino) fenoxi] piridin 2 – carboxilato (1eq) y carbonato de sodio (4eq) en dimethilformamida fue agitada a 20°C bajo nitrógeno por 30 minutos antes de cargar 2 equivalentes de iodometano lentamente a cuenta gotas a la reacción. Después de 2 a 3 horas o hasta que fue determinada la terminación por el HPLC, la reacción fue evaporada bajo presión reducida. La mezcla cruda fue diluida con etilacetato y lavada con agua. La capa orgánica fue secada sobre sulfato de sodio anhidro y evaporada bajo presión reducida para refinar el producto terbutil-4-[3nitro-4-(2,2,2-trifluoro-N-methylacetilamino) fenoxy] -piridin-2-carboxilate como un sólido naranja. MS: MH + = 442.

Paso 5: Síntesis de terbutil 4-[4-(metilamino)-3-nitrofenoxi]piridin-2-carboxilato.

Una solución de terbutil 4-[3-nitro-4-(2,2,2-trifluro-N-metilacetilamino)fenoxil]piridin-2-carboxilato en etanol fue agitada a temperatura ambiente. Una solución 1N de hidróxido de sodio fue lentamente agregada a gotas en la reacción hasta que la conversión fue completa de acuerdo con el HPLC. La reacción fue evaporada bajo condiciones reducidas y luego extractada con etil acetato y lavada con solución acuosa saturada de cloruro de amonio seguida por agua y salmuera. Los extractos orgánicos fueron secados bajo sulfato de sodio anhidro y evaporados bajo presión reducida para refinar el producto como un sólido naranja MS: NH+346.

Paso 6: Sintesis de terbutil 4-[3amino-4(metilamino)fenoxil] piridin-2-carboxilato.

A una solución de terbutil 4-[4-(metilamino)-3nitrofenoxi]piridin-2-carboxilate. (1 eq)se añadió paladio al 10% sobre carbón (0.1 eq) en metanol, fue agitada a temperatura ambiente y soplada con nitrógeno. H_2 fue insuflado a través de la reacción por una o dos horas o hasta que la reacción estuvo terminada por completo determinado por HPLC. N_2 fue insuflado a través de la reacción por 15 minutos antes de que esta fuese filtrada a través de una almohadilla de celita. La almohadilla de celita fue lavada con exceso de metanol seguido por concentración bajo presión reducida para refinar el producto como un sólido amarillento. MS: MH+=316.

Paso 7: Síntesis de terbutil 4-{2-[4-bromofenil)amino]-1metilbenzimidazol-5-iloxi}piridin-2-carboxilato:

Una solucion de la diamina del Paso 6 (1eq) y 4 bromofenil isotiocianato (1eq) en tetrahidrofurano anhidro bajo nitrógeno fue agitada a 20°C por dos a tres horas o hasta cuando

se determinó que la reacción estaba completa por el HPCL. La solución fue tratada con (3 eq) de 1-etil-(3dimetilaminopropil) carbodiimida HCL. La solución agitada fue calentada a 50°C bajo nitrógeno por dos a tres horas o hasta que la reacción terminó por completo determinado por HPLC. La reacción fue evaporada bajo presión reducida y luego diluida con etil acetato y agua. La capa acuosa fue retro-extraida con etil acetato. Las capas orgánicas combinadas fueron lavadas con agua y salmuera. La capa orgánica fue secada sobre sulfato de sodio anhidro y después evaporada bajo presión reducida el material crudo fue purificado por cromatogRafía liquida de contra alta presión para refinar el producto como un polvo café después de liofilización. MS: NH+=495.

Paso 8: Síntesis de 4-{2-[(4-bromofenil)amino]-1metil-1H-benzimidazol-5-il}-N-etilpiridin-2-carboxamida.

Una solución del producto del Paso 7 del ácido trifluoracético fue tratada con dos gotas de agua a temperatura ambiente por 3 a 4 horas o hasta que la reacción estuvo de terminada por completo por HPLC. La reacción fue evaporada bajo presión reducida para refinar el producto como un aceite rojo naranja en rendimiento cuantitativo. MS: MH+= 439.

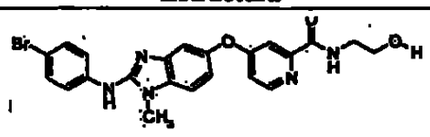
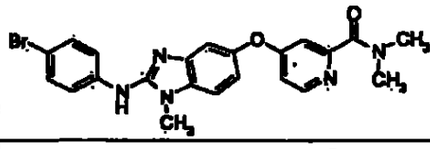
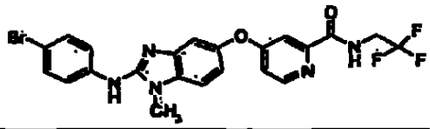
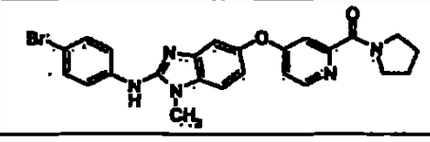
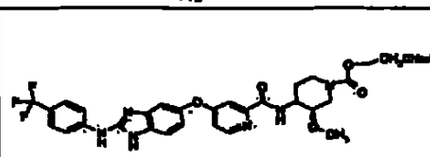
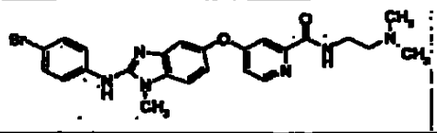
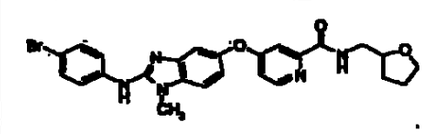
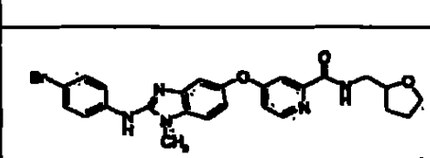
Paso 9: Síntesis de 4-({2-[(4-bromofenil)amino] -1metil-1H-benzimidazol-5-yl}-N-etilpiridin-2-carboxamida.

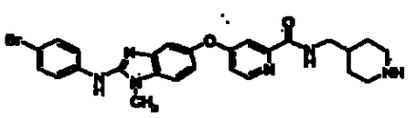
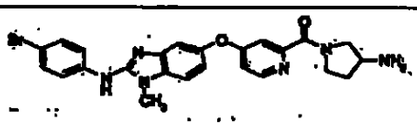
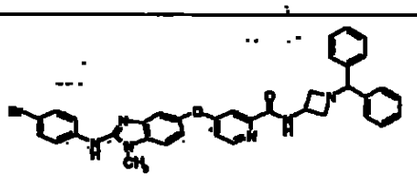
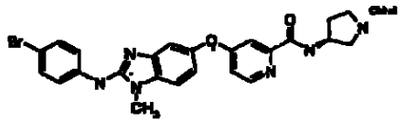
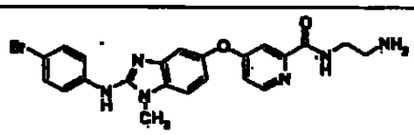
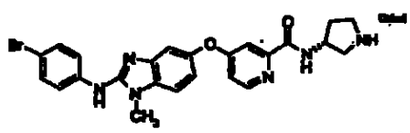
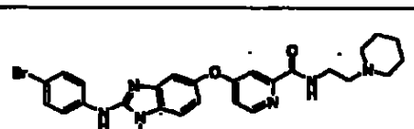
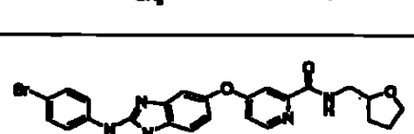
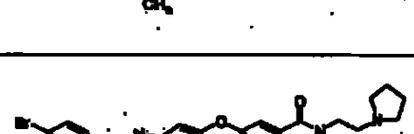
Una solución del compuesto de atrás (1eq) en tetrahidrofurano anhidro (0.5ml) fue tratado con *O*-benzotriazol 1-il N,N,N^1,N^1, tetrametil uranio hexaflurofosfato (2 eq), exceso de diisopropil etil amina y etilamina (1eq.) La reacción fue dejada en agitación bajo nitrógeno entre 12 y 15 horas. La reacción fue evaporada bajo presión reducida y diluida con etil acetato. La capa de etil acetato fue lavada una vez con agua y luego evaporada bajo presión reducida el material crudo fue purificado por cromatogRafía liquida de alta presión y recuperado como sal TFA después de liofilización MS. MH+ =466.

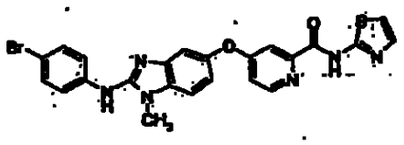
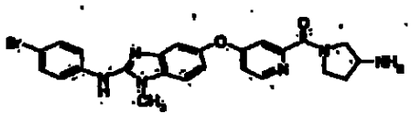
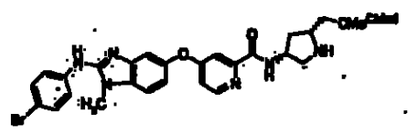
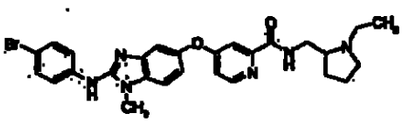
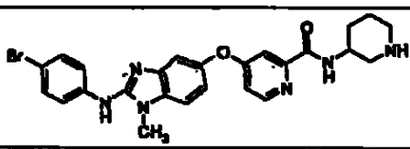
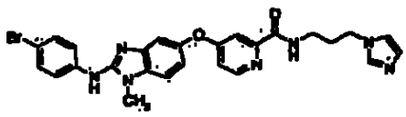
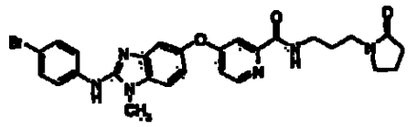
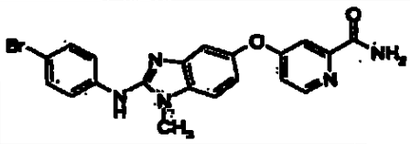
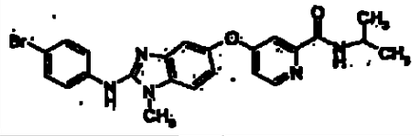
Ejemplo 373 – 447

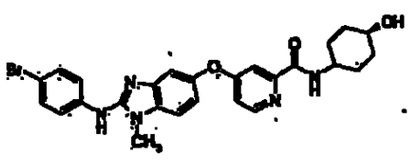
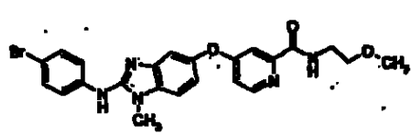
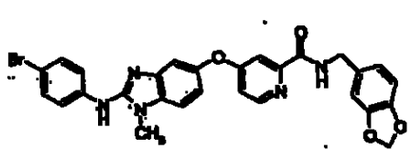
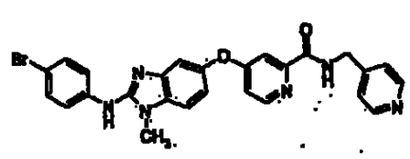
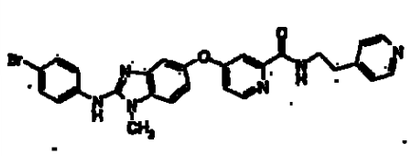
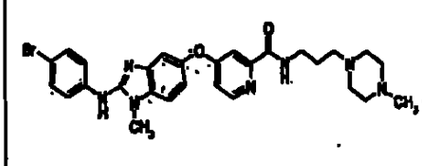
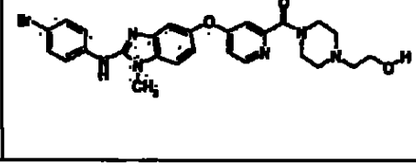
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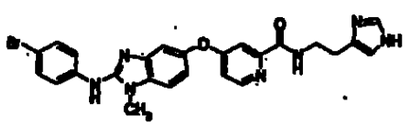
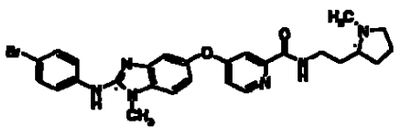
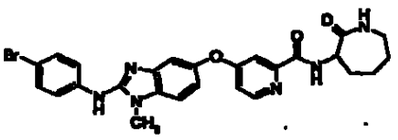
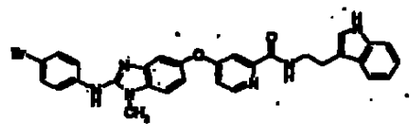
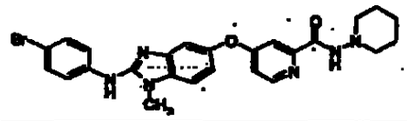
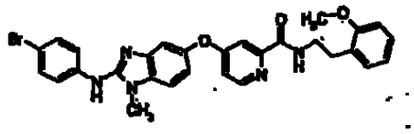
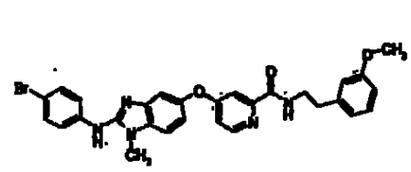
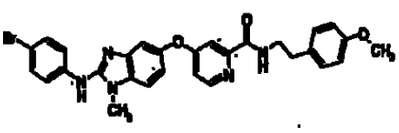
Tabla 4

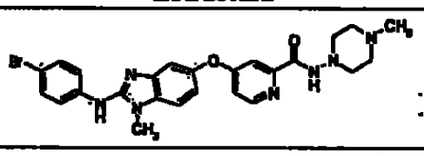
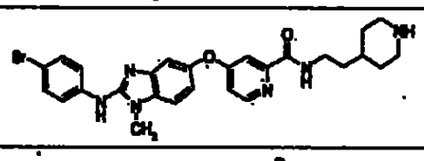
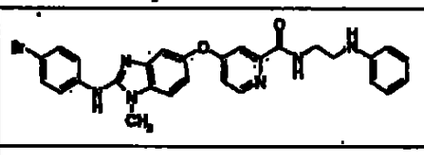
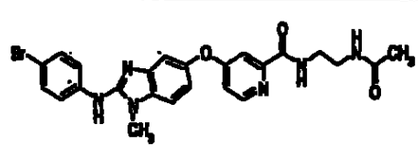
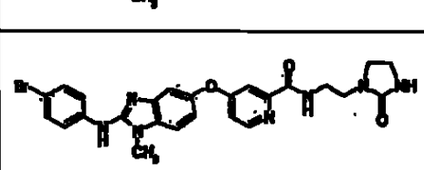
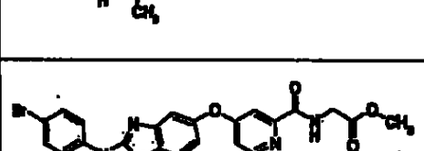
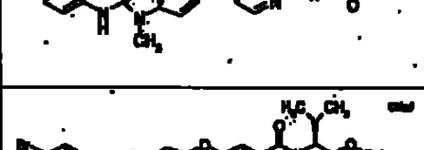
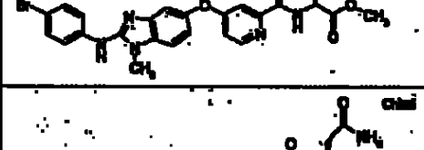
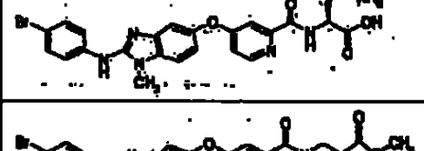
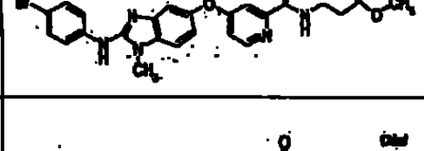
Ejemplo	Estructura	Nombre	MH+
373		4-({2-[(4-bromofenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-(2-hidroxietil)piridin-2-carboxamida	482
374		4-({2-[(4-bromofenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N,N-dimetilpiridin-2-carboxamida	466
375		4-({2-[(4-bromofenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N,-(2,2,2-trifluorometil)-piridin-2-carboxamida	521
376		N-(4-bromofenil)-1-metil-5-{[2-(pirrolidin-1-ilcarbonil)-piridin-4-il]oxi}-1H-bencimidazol-2-amina	492
377		Etil(3R)-3-(metiloxi)-4-[({4-[(2-{[4-(trifluorometil)fenil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-il}carbonil)-amino]piperidin-1-carboxilato	599
378		4-({2-[(4-bromofenil)amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-[2-(dimetilamino)etil]-piridin-2-carboxamida	509
379		4-({2-[(4-bromofenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N,-(tetrahidrofuran-2-il-metil)piridin-2-carboxamida	522
380		4-({2-[(4-bromofenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N,-(2-morfolin-4-iletil)-piridin-2-carboxamida	551

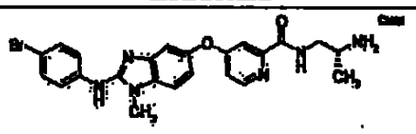
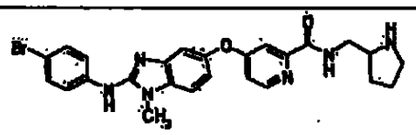
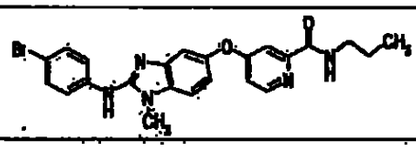
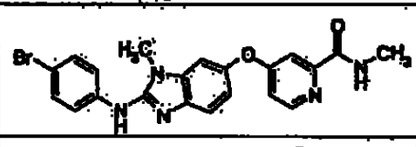
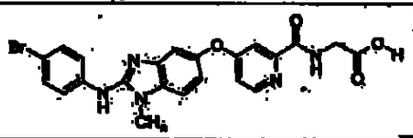
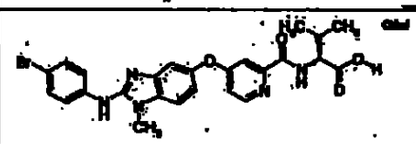
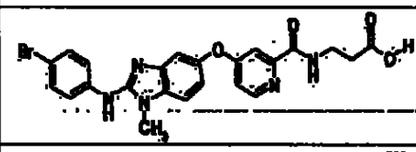
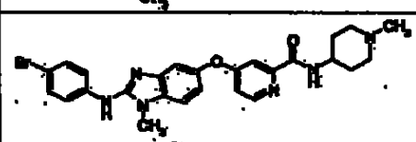
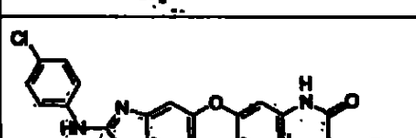
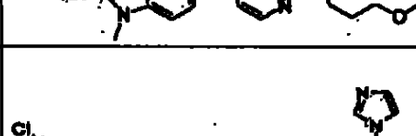
Ejemplo	Estructura	Nombre	MH+
381		4-({2-[(4-bromofenil) amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N,-(piperidin-4-ilmetil)-piridin-2-carboxamida	535
382		5-({2-[(4-bromofenil)amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-(piperidin-4-ilmetil)-piridin-2-carboxamida	507
383		4-({2-[(4-bromofenil)amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-[1-(difenilamino)-azetidin-3-l]piridin-2-carboxamida	659
384		N-((3S)pirolidin-3-il)(4-{2-[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil)) carboxamida	507.0
385		N-(2-aminoetil)(4-{2-[(4-bromo-fenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil))carboxamida	481.0
386		N-((3R)pirolidin-3-il)(4-{2-[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil)) carboxamida	507.0
387		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-(2-piperidiletil)-carboxamida	549.1
388		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-(2-oxolan-2-ilmetil)-carboxamida	522.0
389		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-(2-pirrolidiniletil)-carboxamida	535.1

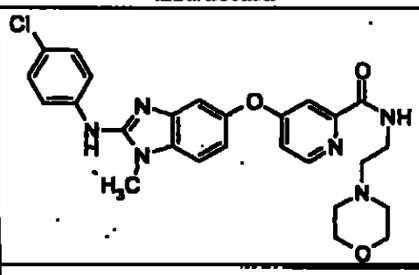
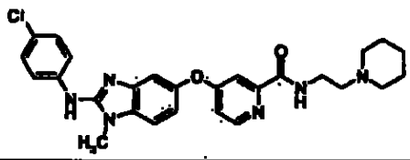
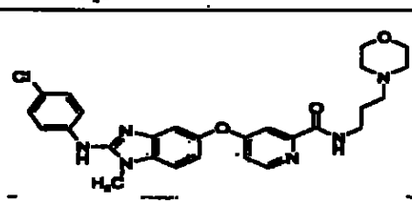
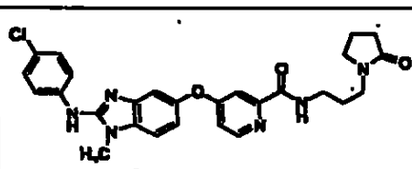
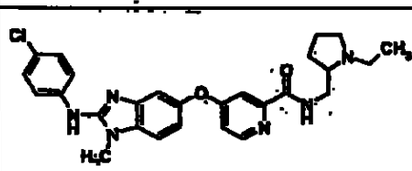
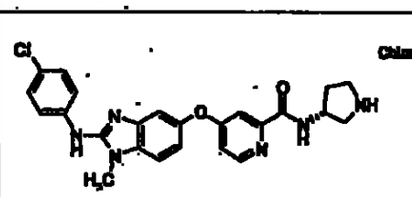
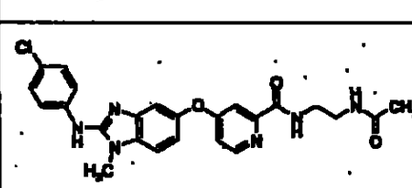
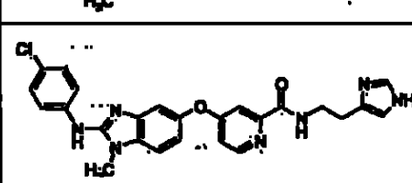
Ejemplo	Estructura	Nombre	MH+
390		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-(1,3-tiazol-2-il)-carboxamida	521.0
391		3-aminopirrolidinil-4-{2-[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil)cetona	507.0
392		N-[(3R, 5R)-5-5(metoximetil)-pirrolidin-3-il](4-{2-[(4-bromo-fenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil))carboxamida	551.1
393		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-[(1-etilpirrolidin-2-il)metil]carboxamida 83 BORRAR	549.2
394		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-(3-piperidil)-carboxamida	521.0
395		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-(3-imidazolilpropil)-carboxamida	546.4
396		(4-{2-[{4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-[3-(2-oxo-pirrolidinil)propil]carboxamida	563.4
397		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}-piridin-2-carboxamida	438.1
398		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(metiletil)-carboxamida	480.3

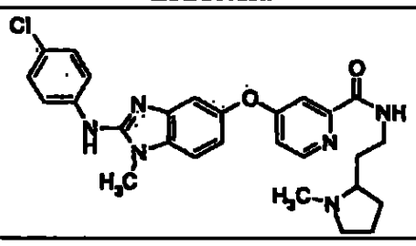
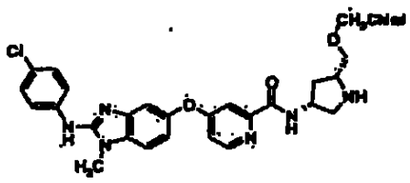
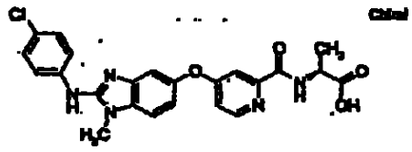
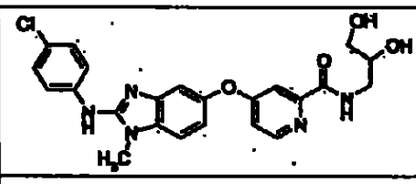
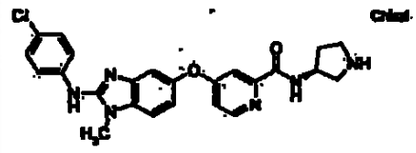
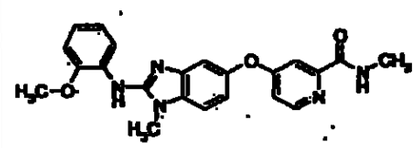
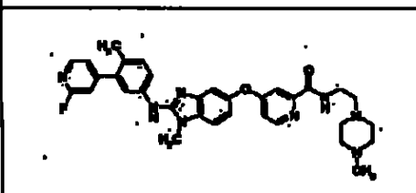
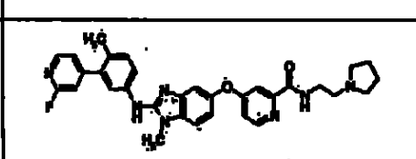
Ejemplo	Estructura	Nombre	MH+
399		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(4-hidroxi-cicloexil)-carboxamida	536.4
400		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-metoxietil)-carboxamida	496.3
401		N-(2h-benzo[d]1,3-dioxolen-5-ilmetil)(4-{2-[(4-bromofenil)-amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-carboxamida	572.4
402		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(4-piridilmetil)-carboxamida	529.3
403		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-(4-piridil)etil)-carboxamida	543.4
404		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[3-(4-metil-piperazinil)propil]-carboxamida	578.5
405		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil)-N-(2-oxietil)piperazinil-quetona	532.4

Ejemplo	Estructura	Nombre	MH+
406		4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-imidazol-4-iletil)-carboxamida	432.4
407		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[2-(1-metil-pirolidin-2-il)etil]-carboxamida	549.1
408		4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-oxoazaperhidroepin-3-il)-carboxamida	549.1
409		4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-indol-3-iletil)-carboxamida	581.4
410		4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-piperidilcarboxamida	521.1
411		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[2-(2-metoxifenil)etil]-carboxamida	572.1
412		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[2-(3-metoxifenil)etil]-carboxamida	572.4
413		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[2-(4-metoxifenil)etil]-carboxamida	572.4

Ejemplo	Estructura	Nombre	MH+
414		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(4-metilpiperazinil)-carboxamida	536.1
415		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-(4-piperidil)etil)-carboxamida	549.4
416		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[2-(fenilamino)etil]-carboxamida	557.4
417		N-{2-[(-{2-[(4-bromofenil)-amino]-1-metilbencimidazol-5-iloxi}-2-piridil)carbonilamino]-etil}acetamida	523.4
418		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[2-(2-oxo-imidazolidinil)etil]-carboxamida	550.4
419		Metil-2-[(4-{2-[(4-bromofenil)-amino]-1-metilbencimidazol-5-iloxi}-2-piridil)carbonilamino]-acetato	510.3
420		Metil(2S)-2[(4-{2-[(4-bromo-fenil) amino]1-metil-bencimidazol-5-iloxi}(2-piridil))carbonilamino]-3-betilbutanoato	552.4
421		(2S)-2-[(4-{2-[(4-bromo-fenil) amino]1-1-metil-bencimidazol-5-iloxi}(2-piridil))carbonilamino]-3-acido carbamoilpropanoico	553.3
422		Metil-3-[(4-{2-[(4-bromo-fenil)-amino]-1-metil-bencimidazol-5-iloxi}-2-piridil)-carbonilamino]-propanoato	524.3
423		N-((2S)-2-aminopropil)(4-{2-[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil))carboxamida	495.3

Ejemplo	Estructura	Nombre	MH+
424		N-((2R)-2-aminopropil)(4-{2-[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil)) carboxamida	495.3
425		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(pirolidin-2-il-metil)-carboxamida	521.4
426		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-propilcarboxamida	480.3
427		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-metilcarboxamida	452.1
428		2-[(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}-2-piridil)caronilamino]ácido acético	496.31
429		(2S)-2-[(4-{2-[(4-bromofenil)-amino]-1-metilbencimidazol-5-iloxi}(2-piridil))carbonilamino]-ácido-3-metilbutanoico	538.1
430		3-[(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}-2-piridil)caronilamino]ácido propanoico	510.1
431		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(1-metil(4-piperidil))-carboxamida	535.1
432		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(3-metoxipropil)-carboxamida	466.1
433		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(3-imidazolilpropil)-carboxamida	502.1

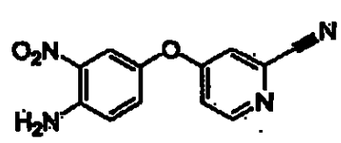
Ejemplo	Estructura	Nombre	MH+
434		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-morfolin-4-il-etil)-carboxamida	507.2
435		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-piperidiletil)-carboxamida	505.2
436		(4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(3-morfolin-4-il-propil)-carboxamida	521.2
437		4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[3-(2-oxo-pirrodilinil)propil]-carboxamida	519.2
438		4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-[(1-etilpirrolidin-2-il)metil]-carboxamida	505.2
439		N-((2R)pirrolidin-3-il)(4-{2-[(4-clorofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil))-carboxamida	463.2
440		N-{2-[(4-{2-[(4-clorofenil)-amino]-1-metilbencimidazol-5-iloxi}-2-piridil)caronilamino]-etil}-acetamida	479.2
441		4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil-N-(2-imidazol-4-il-etil)-carboxamida	488.2

Ejemplo	Estructura	Nombre	MH+
442		(4-{2-[(4-clorofenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-[2-(1-metil-pirrolidin-2-il)etil]carboxamida	505.2
443		N-[3R,5R]-5-(metoximetil)-pirrolidin-3-il](4-{2-[(4-cloro-fenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil)carboxamida	507.2
444		(2S)-2-[(4-{2-[(4-clorofenil)-amino]-1-metilbencimidazol-5-iloxi}(2-piridil))carbonilamino]-acido propanoico	466.1
445		N-(2,3-dihydroxipropil)(4-{2-[(4-clorofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil))carboxamida	468.1
446		N-((3S)pirrolidin-3-il(4-{2-[(4-clorofenil)amino]-1-metil-bencimidazol-5-iloxi}(2-piridil))carboxamida	463.2
447 (síntesis como en ejemplo 120a)		(4-{2-[(2-metoxifenil)amino]-1-metilbencimidazol-5-iloxi}(2-piridil))-N-metilcarboxamida	404.1
448 (síntesis como en ejemplo 483)		4-[(2-{[3-(2-fluoropiridin-4-il)-4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(4-metilpiperazin-1-il)etil]-piperidin-2-carboxamida	595.7
448 (síntesis como en ejemplo 483)		4-[(2-{[3-(2-fluoropiridin-4-il)-4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-pirrolidin-1-iletil)piperidin-2-carboxamida	566.7

Ejemplo 450

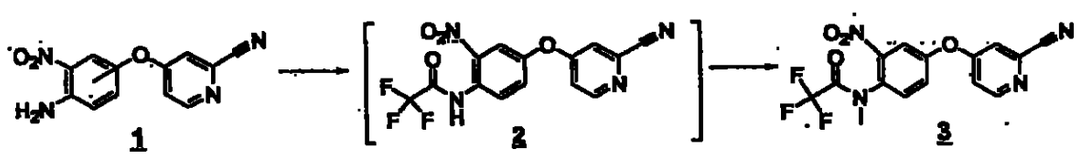
Preparación de (4-clorofenil)-{5-[2-(4,5-dihidro-1H-imidazol-2-il)-Piridin-4-iloxi]-1-metil-1H-benzoimidazol-2-yl}-amina

Paso 1: Síntesis de 4-(4-Amino-3nitro-fenoxi)-puridine-2-carbonitrile:



Carbonato de potasio (9.00g) fue secado en vacío con calentamiento, enfriado a temperatura ambiente bajo nitrógeno. 4-amino3-nitrófenol (3.355g), 4-cloro 2-cianopiridina (3.00 g) y DMSAO (30ml,anhidro) fueron añadidos. El sistema fue agitado bajo nitrógeno, mientras se calentaba a 103°c y mantenido a esta temperatura por 1 hora. La reacción fue luego enfriada a temperatura ambiente, vertida en hielo/H_2O (500ml), el precipitado fue recogido, lavado (H_2O), disuelto (EtoAc), secado (Na_2SO4), filtrado y destilado para dar un sólido. Este fue suspendido (Et2O), recogido, secado al aire 4.10 15g (73.5%) y una segunda porción fue recogida (0.5467g), 10%. Mz=257 (M+1).

Paso 2: Síntesis de N-[4-(2-Ciano-piridin-4-iloxi)-2-nitro-fenil]-2,2,2-trifluoro-N-metilacetamida.

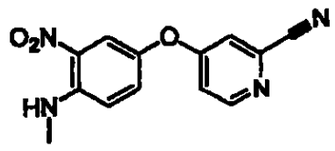


Carbonato de potasio (1.6g) fue secado en vacío con calentamiento, enfriado a temperatura ambiente y suspendido en diclorometano (30ml) con 4-(4-amino-3nitro-

fenoxi)piridin-2-carbonitrilo (2.005g) bajo nitrógeno. Este fue enfriado a 0 grados C y se añadió TFAA (2.2 ml). El material inicial se solubilizó a medida que se fueron haciendo las adiciones. Después de 10 minutos a 0 grados C la mezcla fue diluida con diclorometano, lavada (H_2O, NaCL, acuoso), secada (K_2CO_3), filtrada y secada dando una espuma amarilla. M/z = 353 (M+1). El producto fue usado sin purificación.

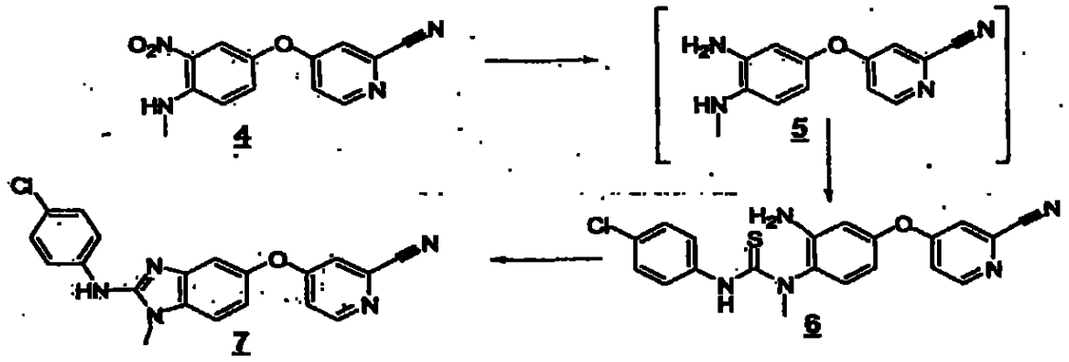
Iodometano (0.53ml) fue añadido a una suspensión de carbonato de potasio (1.858g) en DMF (30ml) que contiene un compuesto 2 (≈7.8mmol) bajo nitrógeno. La suspensión fue agitada a temperatura ambiente toda la noche luego vertida en H_2O (300ml), extractada (Et_2O, 3x 150ml), la combinación de extractos fueron lavados (H_2O, NaCL acuoso), secados (carbonato de potasio) filtrados y despojados dando un aceite naranja 7.4922 g). M/z =367 (M+1).

Paso 3: Síntesis de 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-carbonitrilo:



NaOH (1ml,1NaQ) fue añadido a cuenta gotas a una solución de N-[4-(2-ciano-piridin-4-iloxi)-2-nitrofenil]-2,2,2-trifluoro-N-metil-acetamida (440mg) en etanol (6ml) a temperatura ambiente. Después de 40 minutos la mezcla fue diluida en H_2O (20ml) y enfriada a 0° C . Cristales naranjas brillantes fueron recogidos, lavados (H_2O) y secados al aire, 311.1mg (94%). M/z = 271 (M+1).

Paso 4: Síntesis de 4-[2-(4-clorofenilamino)-1-metil-1H-benzoimidazol-5-iloxi].piridina- 2-carbonitrilo:



Paladio sobre carbón (46mg 10% w/w) fue suspendido en MeOH (2mL) bajo nitrógeno. La suspensión resultante fue añadida bajo nitrógeno, a una suspensión de 4-(4-metilamino-3-nitrofenoxil)-piridin-2-carbonitrilo (311mg) en MeOH (3ml) a temperatura ambiente. La atmósfera fue intercambiada con H_2 y el sistema agitado vigorosamente bajo 1 atm. de H_2 por 1 hora. Luego se intercambio por nitrógeno y la mezcla fue filtrada (celita) y el filtrado fue usado sin completa purificación en la siguiente reacción. M/z 2421 M+1.

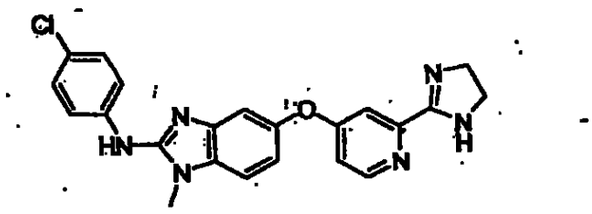
4-clorofenil iciotiozanato (200mg) fue añadido a una solución del compuesto 5 en metanol (10ml). La solución fue agitada a reflujo por 2 horas. Iodometano (71microlitros) fue añadido y agitado continuamente a 67°C toda la noche. La mezcla fue luego enfriada a temperatura ambiente, evaporada a sequedad y el residuo cromatogRafiado (0.5%) NH4OH 5% metanol, 94.5% diclorometano en silica gel).para aislar un compuesto de RF=0.29 (325ml). Este fue cristalizado a partir de diclorometano /eter para dar 127 ml. M/z = 376 (M+1).

1HNMR (MeOH)-d4)

9.40ppm	s(b)		(1H)
8.55ppm	d,d	H=5.7, 0.6 Hz	(1H)
7.62ppm	m		(2h)
7.42ppm	d,d	J=2.5,0.6Hz	(1H)
7.43ppm	d		(1H)
7.37ppm	m		(2h)
7.21ppm	d	J=2.0Hz	(1H)
7.15ppm	d,d	J=5.9,2.5Hz	(1H)

6.97ppm	d,d	J=8.4,2.2hz	(1H)
3.80ppm	s		(3H)

Paso: 5 Síntesis de (4-cloro-fenil)-{5-[2-(4,5-dihidro-1H-imidazol-2-il)-piridin-4-iloxi]-1-metil-1-H- benzoimiazol-2-il}amina:



H_2SO_4 (454 mg) fue añadido cuidadosamente a una suspensión de 4-[2-(4-clorofenilamino)-1-metil-1H-benzomidazol-5-iloxil]-piridin-2-carbonitrile (60.0mg) en etilendiamina (0.50 ml). El sistema fue agitado a temperatura ambiente por 72 horas y luego vertido sobre hielo/NaHCO3. El producto sólido fue recogido, lavado (H_2O) secado al aire, 59.8mg. M/z= 419(M+1).

Ejemplo 451

Síntesis de (4-{2-[(4-bromofenil)amino]benzoxazol-5-iloxi}-(2-piridin))-N-metilcarboxamida

Paso 1: Síntesis de 2-amino-4-metoxifenol

La mezcla conteniendo 4 metoxi-2-nitrofenol en metanol con una cantidad catalítica de 10% Pd/ fue hidrogenada hasta que desapareció el color amarillo para dar 2-amino 4-metoxifenol. MS :NH+ =140.

Paso 2: Síntesis 5-metoxi benzoxazol 2- tiol.

Una mezcla conteniendo 2 amino 4 metoxifenol (1 eq). y ácido O-etil xántico, sal potasica (1.1 eq) en piridina fue reflujada por dos horas .La mezcla resultante fue vertida en

hielo/agua conteniendo HCL para producir el 5-metoxibenzoxazol 2-tiol como un sólido café claro. MS: MH+=182.

Paso 3: Síntesis de 2 cloro 5-metoxi benzoxazol

La mezcla que contiene 5 metoxi benzoxazol-2-tiol fue calentada en cloruro de tionil con una gota de DMF. La mezcla resultante fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue lavada con salmuera, secada y concentrada. La purificación sobre una columna de silica gel dió 2-cloro-5-metoxibenzoxazol como un sólido blanco. MS: MH+=184.

Paso 4: Síntesis de (4-bromofenil)(5-metoxibenzoxazol-2-il)amina.

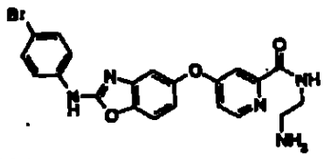
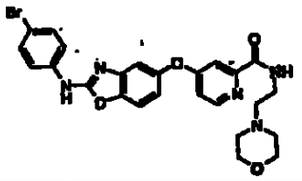
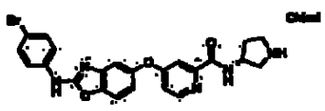
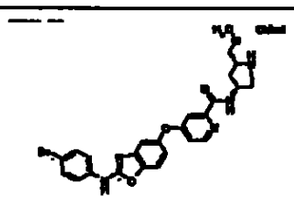
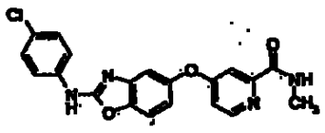
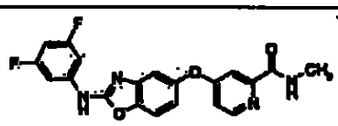
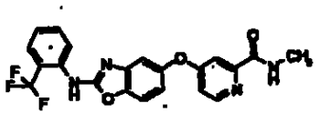
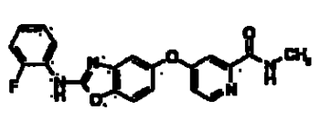
Una mezcla que contiene 2-cloro-5-metoxibenzoxazol (1eq), 4-bromoaniline (2eq) y diisopropil-etilamina fue recirculada en dimetil formamida. La mezcla resultante fue concentrada y dividida entre etilacetato y H_2O. La capa orgánica fue lavada con salmuera y secada la purificación sobre silica gel dió (4-bromofenil)(5-metoxibenzoxazol-2il)amina. MS: MH+=305.

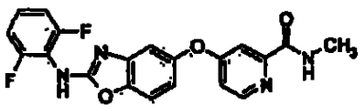
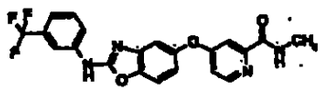
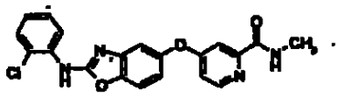
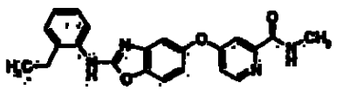
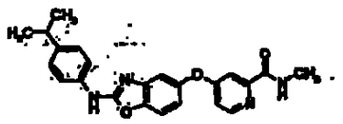
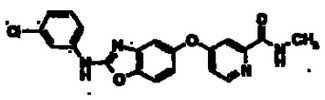
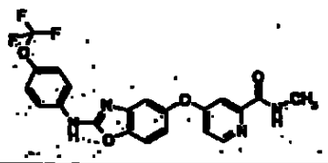
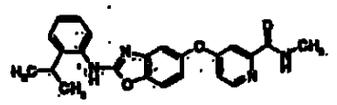
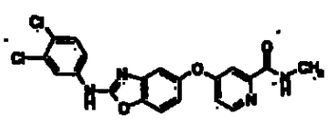
Paso 6: Síntesis de (4-{2-[(4,bromofenil)amino]benzoxazol-5-iloxi}-(2-piridil))-N-metilcarboxamida.

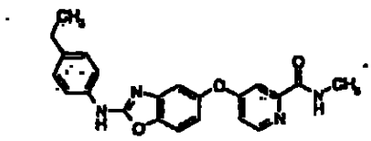
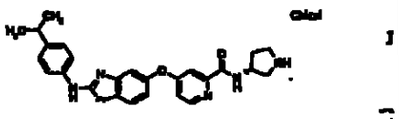
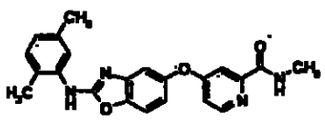
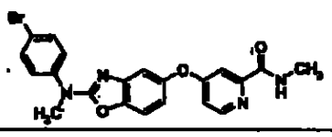
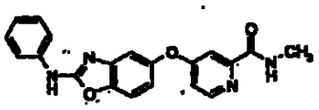
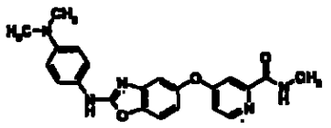
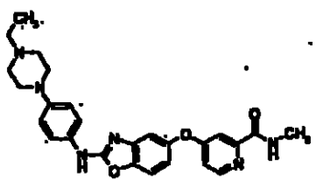
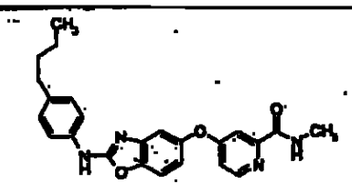
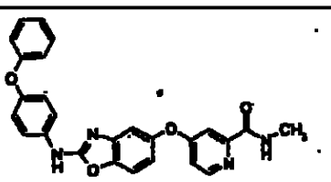
Una mezcla conteniendo (4-{2-[(4,bromofenil)amino]benzoxazol-5-ol} (1 eq), bis (trimetilsilil)amida de potasio (4 eq) fue agitada en dimetil formamida por 20 minutos a temperatura ambiente. A esta mezcla se adicionó (4-cloro(2-piridil)-N-metilcarboxamida (1eq) en carbonato de potasio (1.2eq) y se llevó al microondas por 6 minutos a 150°C. La mezcla reaccionante fue luego concentrada y dividida en etil acetato y agua. La capa orgánica fue separada y lavada con salmuera, secada, filtrada y concentrada. La purificación sobre prep. LC dió el producto deseado MS: MH+=439.

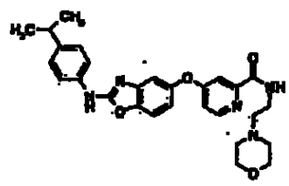
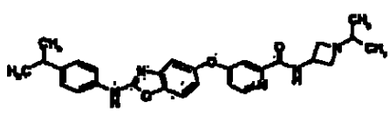
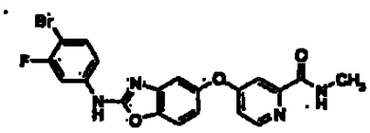
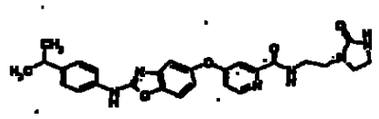
Los compuestos mostrados en la siguiente Tabla 5 (ejemplos 452-481) fueron preparados a partir de los procedimientos descritos en los ejemplos 449 –451.

Tabla 5

Ejemplo	Estructura	Nombre	MH+
452		N-(2-aminoetil)-4-({2-[(4-bromo-fenil)amino]-1,3-benzoxazol-5-il}oxi)piridin-2-carboxamida	469.3
453		4-({2-[(4-bromofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-(2-morfolin-4-iletil)piridin-2-carboxamida	539.4
454		4-({2-[(4-bromofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-[(3R)-pirrolidin-3-il]piridin-2-carboxamida	495.3
455		4-({2-[(4-bromofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-{(3R,5R)-5-[(metiloxi)metil]pirrolidin-3-il}piridin-2-carboxamida	539.4
456		4-({2-[(4-clorofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metil-piridin-2-carboxamida	395.8
457		4-({2-[(3,5-difluorofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metilpiridin-2-carboxamida	397.4
458		N-metil-4[(2-{[2-(trifluorometil)fenil]amino}-1,3-benzoxazol-5-il)oxi]piridin-2-carboxamida	429.4
459		4-({2-[(2-fluorofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metilpiridin-2-carboxamida	379.4

Ejemplo	Estructura	Nombre	MH+
460		4-({2-[2,6-difluorofenil)amino] -1,3-benzoxazol-5-il}oxi)-N-metilpiridin-2-carboxamina	397.4
461		N-metil-4-[(2-{[3-(trifluoro-metil)fenil]amino}-1,3-benzaxol-5-il)oxi]piridin-2-carboxamida	429.4
462		4-({2-[(2-clorofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metil-piridin-2-carboxamida	395.8
463		4-({2-[(2-etilfenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metil-piridin-2-carboxamida	389.4
464		N-metil-4-[(2-{[4-(1-metil-etil)fenil]amino}-1,3-benzaxol-5-il)oxi]piridin-2-carboxamida	403.5
465		4-({2-[2,6-clorofenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metil-piridin-2-carboxamina	395.8
466		N-metil-4-{[(2-({4-[(trifluoro-metil)oxi]fenil}amino)-1,3-benzoxazol-5-il]oxi}piridin-2-carboxamida	445.4
467		N-metil-4-[(2-{[2-(1-metil-etil)fenil]amino}-1,3-benz-oxazol-5-il)oxi]piridin-2-carboxamina	403.5
468		4-({2-[3,4-difluorofenil)amino] -1,3-benzoxazol-5-il}oxi)-N-metilpiridin-2-carboxamina	430.3

Ejemplo	Estructura	Nombre	MH+
469		4-({2-[(4-etilfenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metil-piridin-2-carboxamida	389.4
470		4-[(2-{[4-(1-metilletil)fenil]-amino}-1,3-benzoxazol-5-il)oxi]-N-[(3R)-pirrolidin-3-il]piridin-2-carboxamida	458.5
471		4-({2-[(2,5-dimetilfenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metilpiridin-2-carboxamina	389.4
472		4-({2-[(4-bromofenil)(metil)-amino]-1,3-benzoxazol-5-il}oxi)-N-metilpiridin-2-carboxamida	454.3
473		N-metil-4-{[2-(fenilamoni)-1,3-benzoxazol-5-il]oxi}piridin-2-carboxamida	361.4
474		4-[(2-{[4-(dimetilamino)fenil]-amino}-1,3-bemzoxazol-5-il)oxo]-N-metilpiridin-2-carboxamida	404.4
475		4-[(2-{[4-(4-etilpiperazin-1-il)-fenil]amino}-1,3-benzoxazol-5-il)oxi]-N-metilpiridin-2-carboxamida	473.5
476		4-({2-[(4-butilfenil)amino]-1,3-benzoxazol-5-il}oxi)-N-metil-piridin-2-carboxamida	
477		N-metil-4-[(2-{[4-(feniloxi)-fenil]amino}-1,3-benzoxazol-5-il)oxi]piridin-2-carboxamida	453.5

Ejemplo	Estructura	Nombre	MH+
478		4-[(2-{[4-(1-metiletil)fenil]-amino}-1,3-benzoxazol-5-il)oxi]-N-(2-morfolin-4-iletil)piridin-2-carboxamida	502.6
479		N-[1-(1-metiletil)azetidin-3-il]-4-[(2-{[4-(1-metiletil)fenil]-amino}-1,3-benzoxazol-5-il)oxi]-piridin-2-carboxamida	486.6
480		4-({2-[(4-bromo-3-fluorofenil)-amino]-1,3-benzoxazol-5-il}oxi)-N-metilpiridin-2-carboxamida	458.3
481		4-[(2-{[4-(1-metiletil)fenil]-amino}-1,3-benzoxazol-5-il)oxi]-N-[2-(2-oxoimidazolidin-1-il)-etil]piridin-2-carboxamida	501.6

Ejemplo 482

Síntesis de [4-(2-{[4-(dimetilamino)fenil]amino-1-metil bencimidazol-5-iloxi)(2-piridil)}-N-(2-pirrolidiniletil)carboxamida

Paso 1. Síntesis del 4-(2-{[4-(dimetilamino)fenil]amino-1-metilbencimidazol-5-iloxi)piridin-2-ácido carboxílico

A ter-butil-4-[3-amino-4-(metilamino)fenoxi]piridin-2carboxilato (1eq) en metanol fue añadido 4-(dimetilamino)bencenisotiocianato (1eq) y se agitó a temperatura ambiente por 16 h. La formación de la correspondiente tioúrea fue seguida por LC/MS. La mezcla fue luego concentrada y se le añadió tetrahidrofurán y 1-etil-(3-dimetilaminopropil) carbodimida-hidrocloruro (2eq) y agitado a temperatura ambiente por 16 h. ter–butil-4-(2-{[4-(dimetilamino)fenil]amino-1-metilbencimidazol-5-iloxi)piridin-2-carboxilato sale de la mezcla reaccionante. A este se agrega cloruro de metileno y ácido trifluoroacético y agitado a

temperatura ambiente toda la noche. Resultando 4-(2-{[4-(dimetilamino)fenil]amino-1-metilbencimidazol-5-iloxi)piridin-2-ácido carboxílico purificado por cromatogRafía preparativa. MS: MH += 403.

Paso 2. Síntesis de [4-(2-{[4-(dimetilamino)fenilamino-1-metil-bencimidazol-5-iloxi}(2-piridil)]-N-(2-pirrolidiniletil)carboxamida:

Al ácido carboxílico [4-(2-{[4-(dimetilamino)fenilamino-1-metilbencimidazol-5-iloxi}-piridin-2- (1eq) en tetrahidrofuràn fue añadido 2-pirrolidiniletilamina (2eq), HBTU (2eq) y N,N-diisopropiletilamina (4eq) y agitado a temperatura ambiente por 16 h.. La mezcla fue luego concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y la cromatogRafía preparativa dió [4-(2-{[4-(dimethilamino)fenil]lamino-1-metilbencimidazol-5-iloxi]2-piridil}-N-(2-pirrolidinetil)carboxamida. MS: MH += 498.

Ejemplo 483

Síntesis de [4-(2-{[4-bromo-3-metilfenil]amino-1-metil bencimidazol-5-iloxi}(2-piridil))-N-(2-pirrolidiniletil)]carboxamida

Paso 1. Síntesis del ácido carboxílico 4-{2-[(4-bromo-3-metilfenil)amino]-1-metil-bencimidazol-5-iloxi}piridin-2.

A ter-butil14-[3-amino-4-(metilamino)fenoxi]piridin-2-carboxilato (1eq) en metanol fue añadido 4-bromo-3-metilbencenisocianato (1eq) y agitado a temperatura ambiente por 16 h. La formación de la correspondiente tioúrea fue seguida por LC/MS. Luego fue adicionado iodometano (1eq) y calentado a 60°C por 2 h. La formación de ter-butil-4-(2{[4-bromo-3-metilfenil]amino}-1-metilbencimidazol-5-iloxi)piridin-2-carboxilato. fue seguida por LC/MS. A este se le añadió cloruro de metileno y ácido trifluoroacético y agitado a temperatura ambiente toda la noche. Resultando el ácido carboxílico 4-(2-{[4-bromo-3-metilfenilamino]-1-metilbencimidazol-5-iloxi}piridin-2. Fue purificado por cromatogRafía preparativa. MS:MH+= 452.

Paso 2. Síntesis de [4-(2-{[4-bromo-3-metilfenil)amino-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-(2-pirrolidiniletil)carboxamida.

Al ácido carboxílico 4-(2-{[4-bromo-3-metilfenilamino)-1-metilbencimidazol-5-iloxi)-piridin-2 (1eq) en tetrahidrofurán se le añadió 2- pirrolidiniletilamine (2eq), HBTU (2eq) y N,N-diisopropiletilamina (4eq) y agitado a temperatura ambiente por 16 h. La mezcla fue luego concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y por cromatogRafía preparativa dió [4-(2-{[4-bromo-3-metilfenil]amino-1-metilbencimidazol-5-iloxi}-(2-piridil))-N-(2-pirrolidiniletil)]carboxamida. MS:MH+ = 549.

Ejemplo 484

Síntesis de [4-(2-{[2-fluoro-5-(trifluormetil)fenil)amino]-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-(2-pirrolidiniletil]carboxamida

Paso 1. Síntesis del ácido carboxílico 4-{2-[(2-fluoro-5-(trifluorometil)fenil)amino]-1-metilbencimidazol-5-iloxi}piridin-2.

A ter-butil 4-[3-amino-4-(metilamino)fenoxi]piridin-2-carboxilato (1eq) en metanol fue añadido 2-fluoro-5-(trifluorometil)bencenisocionato (1eq) y agitado a temperatura ambiente por 16 h. La formación de la correspondiente tioúrea fue seguida por LC/MS. Luego fue añadido iodometano (1eq) y calentado a 60°C por 2 h. La formación del ter-butil 4-{2-[(2-fluoro-5-(trifluorometil)fenil)amino]-1-metilbencimidazol-5-iloxi}piridina-2-carboxilato fue seguida por LC/MS . A esto en cloruro de metileno se la añadió ácido trifluoroacético y agitado a temperatura ambiente toda la noche. Resultando el ácido carboxílico 4-{2-[(2-fluoro-5-(trifluorometil)fenil)amino]-1-metilbencimidazol-5-iloxi}-piridina-2- Fue purificado por cromatogRafía preparativa. MS:MH+ =456.

Paso 2. Síntesis de [4-(2-{[2-fluoro-5-(trifluorometil)fenil)amino-1-metil-bencimidazol-5-iloxi)(2-piridil)}]-N-(2-pirrolidiniletil)carboxamida :

Ácido carboxílico 4-(2-{[2-fluoro-5-(trifluorometil)fenilamino)-1-metilbencimidazol-5-iloxi)piridin-2 (1 eq) en tetrahidrofurán se le añadió 2-pirrolidiniletilamina (2eq), HBTU (2eq) y N,N-diisopropiletilamina (4eq) y agitado a temperatura ambiente por 16 h. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y la cromatogRafía preparativa dió [4-(2-{[(2-fluoro-5-(trifluorometil)fenil]amino-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-(2 pirrolidiniletil)carboxamida. MS:MH+ =542.

Ejemplo 485

Síntesis de [4-(2-{[4-bromo-3-fluorofenil]amino-1-metilbencimidazol-5-iloxi) (2-piridil)]-N-(2-piperidiletil)-carboxamina

Paso 1. Síntesis de ácido carboxílico 4-{2-[(4-bromo-3-fluorofenil)amino]-1-metil-bencimidazol-5-iloxi}piridin-2.

A ter-butil-4-[3-amino-4(metilamino)fenoxi]piridin-2-carboxilato (1eq) en metanol se le añadió 4-bromo-3-fluorobencenisotiocianante (1eq) y se agitó a temperatura ambiente por 16 h. La formación de la correspondiente tioúrea fue seguida por LC/MS. Se le añadió iodometano (1eq) y fue calentado a 60° C por 2 h. La formación de ter-butil 4-(2-{[4-bromo-3-fluorofenil]amino)-1-metilbencimidazol-5-iloxi}piridin-2-carboxilato fue seguida por LC/MS. A esto, en cloruro de metileno, se le añadió ácido trifluroacético y agitando a temperatura ambiente toda la noche. Resultando 4-(2-[4-bromo-3-fluorofenilamino]-1-metilbencimidazol-5-iloxi)piridina-2-ácido carboxílico que fue purificado por cromatogRafía preparativa. MS: MH+ = 456.

Paso 2. Síntesis de [4-(2-{[4-bromo-3-fluorofenil)amino-1-metilbencimidazol-5-ilox)(2-piridil)]-N-(2-piperidiletil)carboxamida:

Al ácido carboxílico 4-(2-[4-bromo-3-fluorfenil)amino]-1-metilbencimidazol-5-iloxi)piridina-2 (1eq) en tetrahidrofurán se le añadió 2-piperidietilamina (2eq), HBTU (2eq) y

N,N-diisopropiletilamina (4eq) y fue agitado a temperatura ambiente por 16 h. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y la cromatogRafía preparativa dió [4-(2-{[4-bromo-3-fluorofenil]amino-1-metilbencimidazol-5-iloxi)(2-piridil)]-N-(2-piperidiletil)-carboxamina. MS: MH+ = 567.

Ejemplo 486

Síntesis de 4-{1-metil-2-[(4-metilfenil)amino-1-metil-bencinidazol-5-iloxi](2-piridil)} -N-(2-pirrolidiniletil)carboxamina

Paso 1. Síntesis de ácido carboxílico 4-{1-metil-2-[(4-metilfenil)amino]bencinidazol-5-iloxi} piridin-2.

A ter-butil-4-[3-amino-4-(metilamina)fenoxi]piridin-2-carboxilato (1eq) en metanol fue añadido 4-metilbencenisotiocianante (1eq) y agitado a temperatura ambiente por 16 h. La formación de la correspondiente tioúrea fue seguida por LC/MS. A esto se añadió iodometano (1eq) y se calentó a 60°C por 2 h. La formación de ter-butil-4-{1-metil-2-[(4-metilfenil)amino]bencinidazol-5-iloxi}piridina-2-carboxilato fue seguida por LC/MS. A esto en cloruro de metileno se le añadió ácido trifluoro acético y se agitó a temperatura ambiente durante toda la noche. El resultado fue ácido carboxílico 4-{1-metil-2-[(4-metilfenil)-amino]bencinidazol-5-iloxi}piridina-2 el cual fue purificado por cromatogRafía preparativa. MS:MH+ = 374.

Paso 2. Síntesis de 4-{1-metil-2-[(4-metilfenil)amino-1-metil-bencimidazol-5-iloxi](2-piridil)}-N-(2-pirrolidiniletil)carboxamida.

A 4-{1-metil-2-[(4-metilfenil)amino]bencimidazol-5-iloxi}piridina-2-ácido carboxílico (1eq) en tetrahidrofuran se añadió 2-pirrolidiniletilamina (2eq), HBTU (2eq) y N, N-diisopropiletilamina (4eq) y agitado a temperatura ambiente por 16 horas. La mezcla fue entonces concentrada y dividida entre acetato de etil y agua. La capa orgánica fue concentrada

y por cromatogRafía preparativa dió 4-{1-metil-2-[(metilfenil)amino-1-metilbanzimidazol-5-iloxi)(2 piridil)]-N-2-(2-pirrolidiniletil)carboxamida. MS: MH+ = 470.

Ejemplo 487

Síntesis de [4-(2-{[4-etilfenil)amino-1-metilbencimidazol-5-iloxi)(2-piridil)]-N-(2-pirrolidiniletil)carboxamida.

Paso 1: Síntesis de 4-{2-[(4—etilfenil)amino]-1-metilbenzomidazol-5-yloxi}piridina-2-ácido carboxílico.

A ter-butil 4-[3amino-4-(metilamino)fenoxil]piridina-2-carboxilato (1eq) fue añadido en metanol 4-etilbencenisotiocianato (1eq) fue agitado a temperatura ambiente por 16 horas. La formación de la correspondiente tioúrea fue seguida LC/MS. A esto se le añadió iodometano (1eq) y se calentó a 60°C por 2 horas. La formación de terbutil-4-(2-{[4-etilfenil]amino)-1-metilbencimidazol-5-iloxi)piridin–2-carboxilato fue seguido por LC/MS. A esto en cloruro de metileno se le agregó ácido trifluoroacético y agitando a temperatura ambiente toda la noche, resultando 4-(2-{[4-etilfenilamino)-1-metilbencimidazol-5-iloxi)-piridin-2-ácido carboxílico que fue purificado por cromatogRafía preparativa. MS:MH+. = 388.

Paso 2: Síntesis de [4-(2-{[4- etilfenil)amino-1-metilbencimidazol-5-iloxi)(2-piridil)]-N- (2-pirrolidiniletil)carboxamida.

A 4-(-2{[4- etilfenilamino)- 1-metilbencimidazol-5-iloxi)piridin 2 ácido carboxílico (1eq) en tetrahidrofurano le fue añadido 2-pirrolidiniletilamina (2eq), HBTU (2eq) en N,N–diisopropiletilamina (4eq) y fue agitado a temperatura ambiente por 16 horas. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y por

cromatogRafía preparativa dió [4(2-{[4-etilfenil]amino-1-metilbencimidazol-5-iloxi) (2-piridil]-N-(2-pirrolidinil-etil)carboxamida. MS:MH+=484.

Ejemplo 488

Síntesis de [4(2-{[3-(terbutil)fenil)amino-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-(2-pirediletil)carboxamida

Paso 1: Síntesis de ácido 4-{2-[(3-(terbutil)fenil) amino]-1- metilbencimidazol-5-iloxi)(piridina-carboxílico.

A ter-butil-4-[3-amino-4-(metilamino)fenoxi]piridin-2-carboxilato (1eq) en metanol fue añadido 3-(terbutil)bencenisotiocianato (1eq) y agitado a temperatura ambiente por 16 horas. La formación de la correspondiente tioúrea fue seguida por LC/MS. Fue añadido iodometano (1eq) y calentado 60°C por 2 horas. La formación de terbutil4-(2-{[3-terbutil)fenil]amino)-1-metilbencimidazol-5-iloxi)piridin–2-carboxilato fue seguida en LC/MS. A esto en cloruro de metileno fue añadido ácido trifluroacético y agitado a temperatura ambiente toda la noche. El resultado 4-(2-{[3-terbutil)fenilamino]amino)-1-metilbencimidazol-5-iloxi)piridina-2-ácido carboxílico fue purificado por cromatogRafía preparativa. MS: MH+ = 416.

Paso 2: Síntesis de [4-(2-{[3-(terbutil)fenil)amino)-1-metilbencimidazol-5-iloxi)(2-piridil)]-N-(2-piperidiletil)carboxamida

A 4-(2-{[3-(terbutil)fenilamino)-1-metilbencimidazol-5-iloxi)piridin-2- ácido carboxílico(1eq) en tetrahidrofurano fue añadido 2-piperiditilamina (2eq), HBTU (2eq) en N,N-diisopropiletilamina (4eq) y fue agitado a temperatura ambiente por 16 horas. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica concentrada y por

cromatogRafía preparativa dió [4-(2-{[3-(terbutil)fenil]amino-1-metilbencimidazol-5-iloxi)(piridil)]-N- (2—piperidiletil)-carboxamida. MS:MH+=512.

Ejemplo 489

Síntesis de [4-(2-{[4-cloro-3-(trifluorometil)fenil)amino-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-(2-piridiletil)carboxamida.

Paso 1: Síntesis de 4-(2-{[4-cloro-3-(trifluorometil)fenil)amino]-1-metil-bencimidazol-5-iloxi)piridin-2-ácido carboxílico.

A terbutil 4-[3 amino-4-(metilamino)fenoxi]piridin-2-carboxilato (1eq) en metanol fue agregado 4-cloro-3-(trifluorometil)bencenisotiocinato (1eq) y agitado a temperatura ambiente por 16 horas. La formación de la correspondiente tioúrea y seguida por LC/MS. A esto se añadió iodometano (1eq) y calentado 60°C por 2 horas. La formación de terbutil 4-(2-{[4-cloro-3-(trifluorometil)fenil)amino]-1-metilbencimidazol-5-iloxi)piridin-2-carboxilato fue seguida por LC/MS. A esto en cloruro de metileno se le agregó ácido trifluoroacético y agitado a temperatura ambiente toda la noche. Resultando ácido 4-(2-{[4-cloro-3-(trifluorometil)fenil)amino)-1-metilbencimidazol-5-iloxi)piridin-2-ácido carboxílico fue purificado por cromatogRafía. MS:MH+=462.

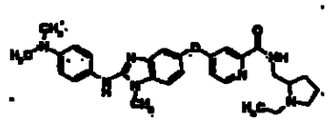
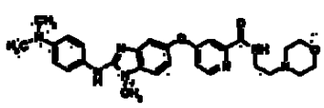
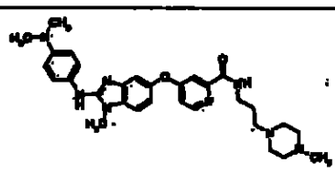
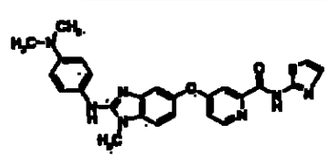
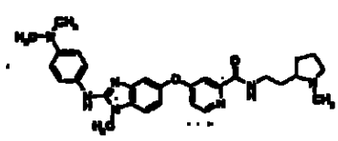
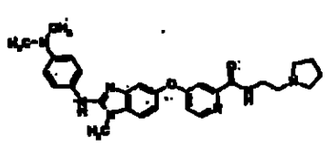
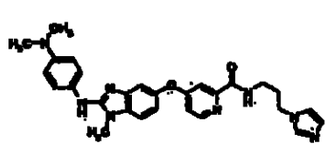
Paso 2: Síntesis de [4-(2-{[cloro-3-(trifluorometil)fenil)amino-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-(2-piperidiletil)carboxamida.

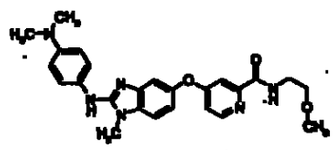
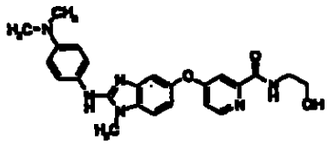
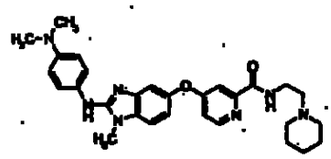
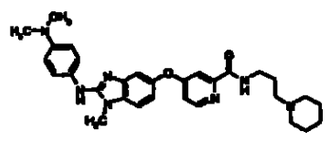
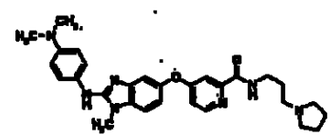
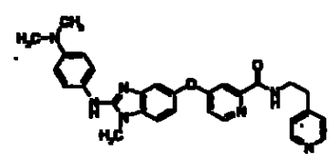
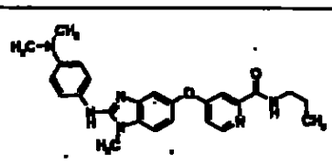
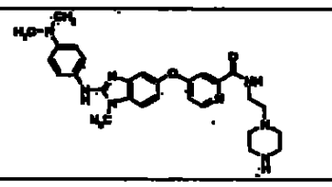
A 4-(2-{[4-cloro-3-(trifluorometil)fenilamino)-1-metilbencimidazol-5-iloxi)-piridin-2-ácido carboxílico(1eq) en tetrahidrofurano fue agregado 2-piperidiletilamina (2eq), HBTU (2eq) y N,N-diisopropiletilamina (4eq) agitando a temperatura ambiente por 16 horas. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada

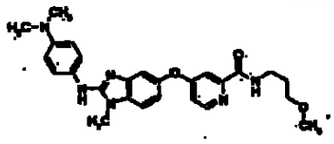
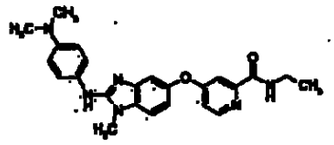
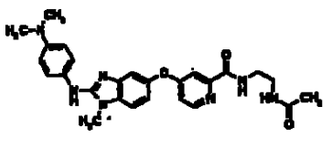
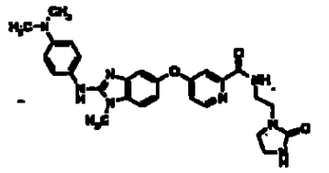
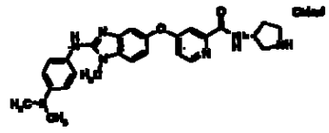
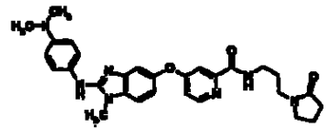
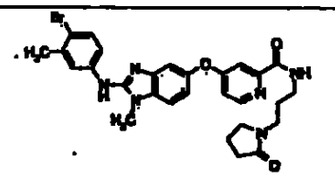
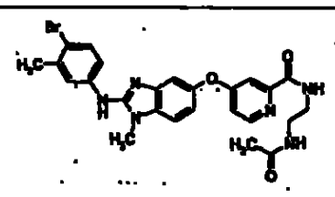
y por cromatogRafía dió [4-(2-{[4-cloro-3-(trifluorometilfenil)amino-1-metilbencimidazol-5-iloxi)(2-piridil)]-N-(2piperidiletil)carboxamida. MS: MH+ = 558.

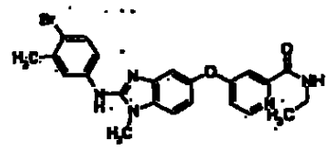
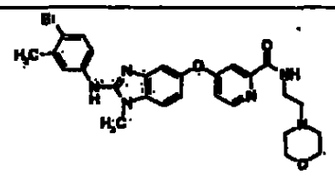
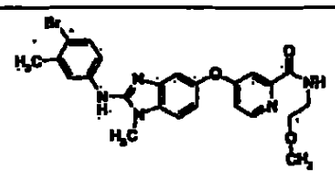
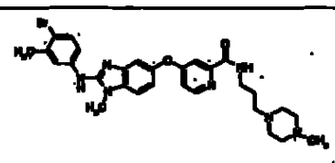
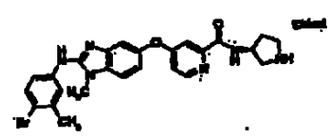
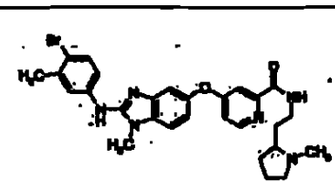
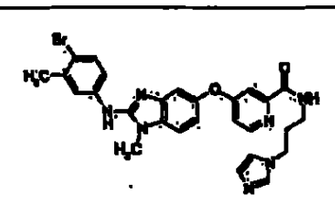
Cada unos de los compuestos listados abajo en la Tabla 6 fueron sintetizados como esta indicado en la columna derecha con el método descrito en uno de los ejemplos 482 – 489.

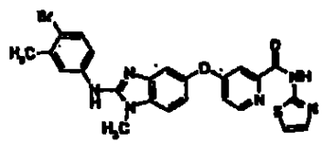
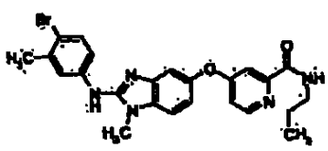
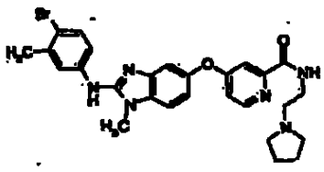
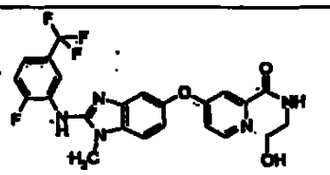
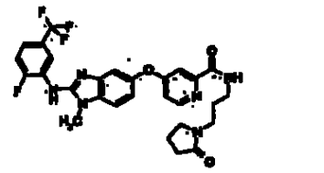
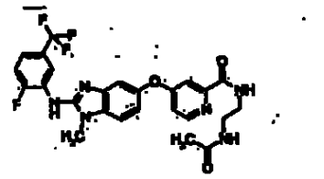
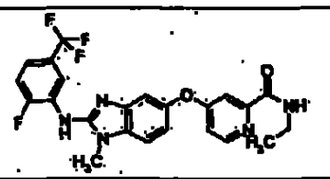
Tabla 6

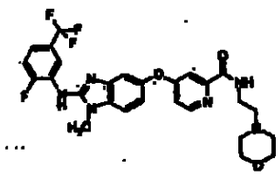
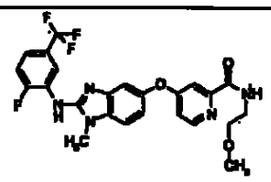
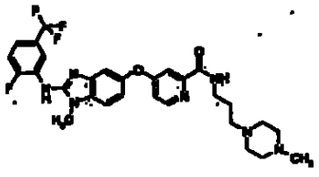
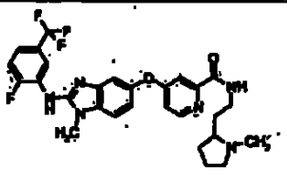
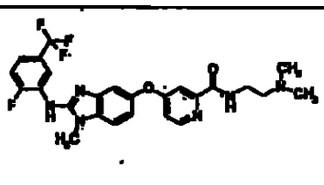
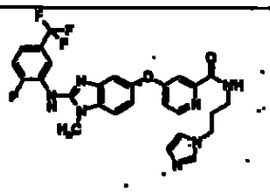
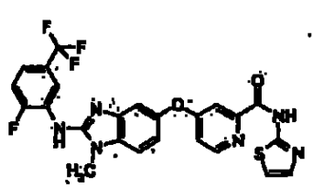
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
490		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[(1-etilpirrolidin-2-il)-metil]piridin-2-carboxamida	514.6	482
491		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-iletil)piridin-2-carboxamida	516.6	482
492		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	543.7	482
493		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-1,3-tiazol-2-ilpiridin-2-carboxamida	586.6	482
494		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2(1-metilpirrolidin-2-il)etil]-piridin-2-carboxamida	514.6	482
495		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-pirrolidin-1-iletil)-piridin-2-carboxamida	500.6	482
496		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(1H-imidazol-1-il)propil]piridin-2-carboxamida	511.6	482

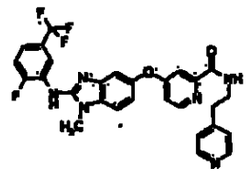
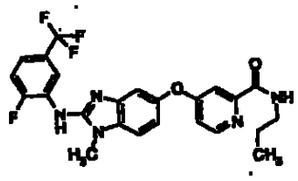
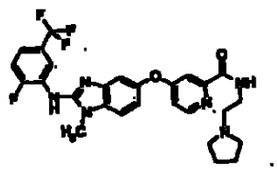
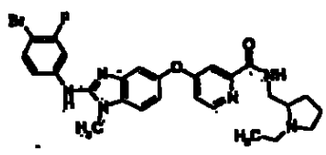
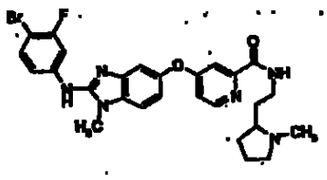
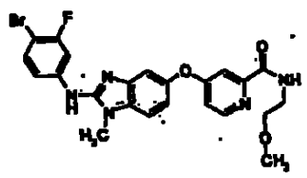
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
497		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(metiloxi)etil]-piridin-2-carboxamida	461.5	482
498		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-hidroxietil)-piridin-2-carboxamida	447.5	482
499		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperidin-1-iletil)-piridin-2-carboxamida	514.6	482
500		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(3-piperidin-1-ilpropil)-piridin-2-carboxamida	528.7	482
501		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(3-pirrolidin-1-ilpropil)-piridin-2-carboxamida	514.6	482
502		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piridin-4-iletil)-piridin-2-carboxamida	508.6	482
503		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-propilpiridin-2-carboxamida	445.5	482
504		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperazin-1-iletil)-piridin-2-carboxamida	515.6	482

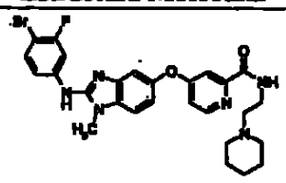
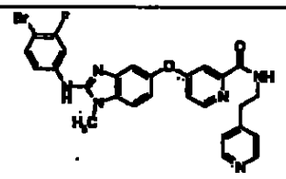
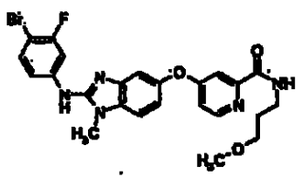
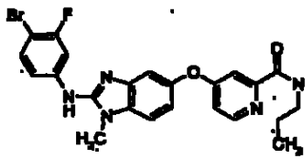
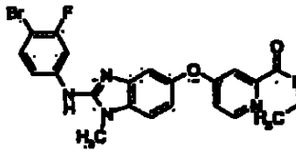
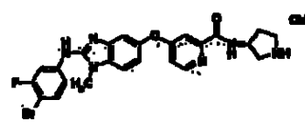
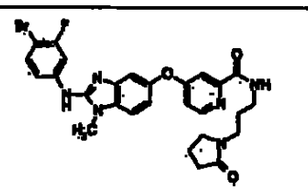
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo:
505		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(metiloxi)propil]-piridin-2-carboxamida	475.6	482
506		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-etilpiridin-2-carboxamida	431.5	482
507		N-[2-(acetilamino)etil]-4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il}oxi]-piridin-2-carboxamida	488.6	482
508		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(2-oxoimidazolidin-1-il)etil]piridin-2-carboxamida	515.6	482
509		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[(3R)-pirrolidin-3-il]piridin-2-carboxamida	472.6	482
510		4-[(2-{[4-(dimetilamino)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(2-oxopirrolidin-1-il)propil]piridin-2-carboxamida	528.6	482
511		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(2-oxopirrolidin-1-il)propil]piridin-2-carboxamida	478.5	483
512		N-[2-(acetilamino)etil]-4-({2-[4-bromo-3-metilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)piridin-2-carboximida	538.4	483

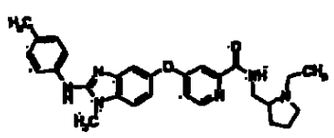
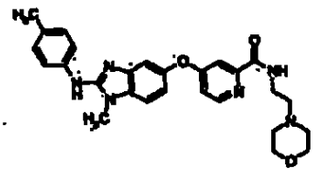
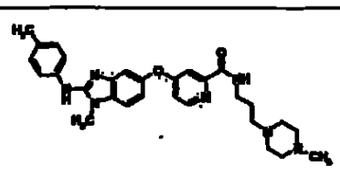
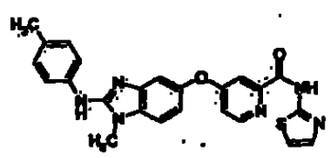
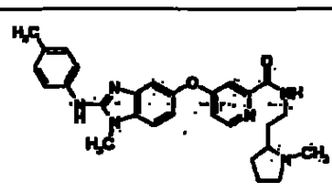
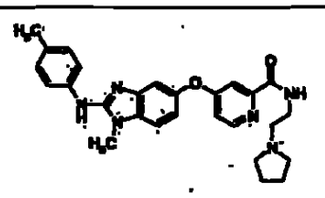
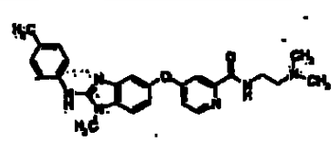
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
513		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-etilpiridin-2-carboxamida	481.4	483
514		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-(2-morfolin-4-iletil)-piridin-2-carboxamida	566.5	483
515		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(metiloxi)etil]-piridin-2-carboxamida	511.4	483
516		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	593.5	483
517		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-[(3R)-pirrolidin-3-il]-piridin-2-carboxamida	522.4	483
518		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1-metil-pirrolidin-2-il)etil]-piridin-2-carboxamida	564.5	483
519		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(1H-imidazol-1-il)propil]-piridin-2-carboxamida	561.5	483

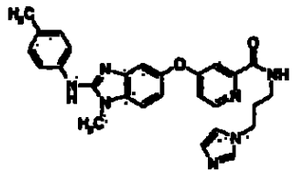
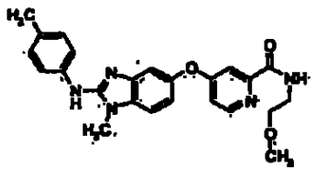
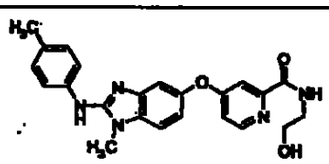
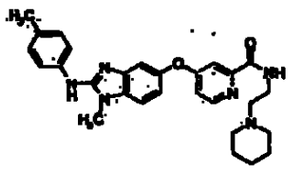
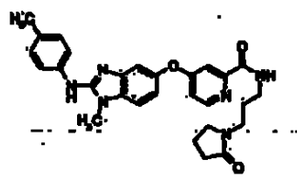
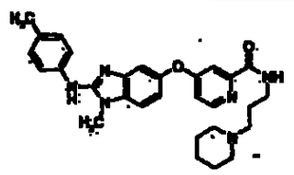
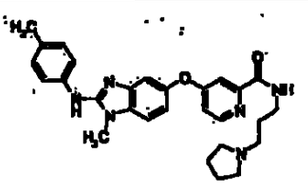
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
520		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-1,3-tiazol-2-il-piridin-2-carboxamida	536.4	483
521		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-propilpiridin-2-carboxamida	495.4	483
522		4-({2-[(4-bromo-3-metilfenil)amino]1-metil-1H-bencimidazol-5-il}oxi)-N-(2-pirrolidin-1-iletil)-piridin-2-carboxamida	550.5	483
523		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-hidroxietil)piridin-2-carboxamida	490.4	484
524		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(2-oxopirrolidin-1-il)propil]-piridin-2-carboxamida	571.5	484
525		N-[2-(acetilamino)etil]-4-[(2-{[2-fluoro-5-(trifluorometil)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	531.5	484
526		N-etil-4-[(2-{[2-fluoro(trifluorometil)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	474.4	484

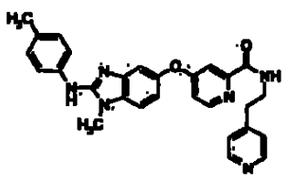
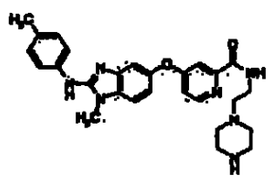
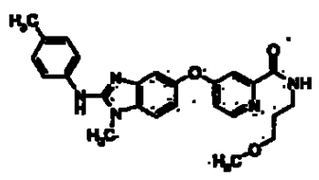
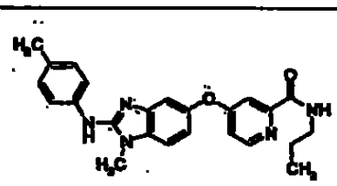
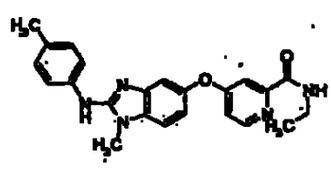
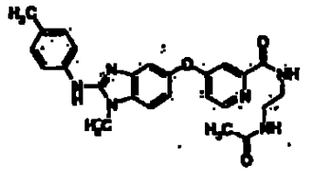
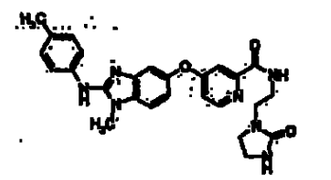
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
527		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-il-etil)piridin-2-carboxamida	559.5	484
528		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(metiloxi)etil-]-piridin-2-carboxamida	504.5	484
529		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	586.2	484
530		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(1-metilpirrolidin-2-il)etil]-piridin-2-carboxamida	557.6	484
531		N-[2-(dimetilamino)-etil]-4-[(2-{[2-fluoro-5-(trifluorometil)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	517.5	484
532		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(1H-imidazol-1-il)-propil]-piridin-2-carboxamida	554.5	484
533		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-1,3-tiazol-2-ilpiridin-2-carboxamida	529.5	484

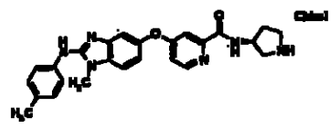
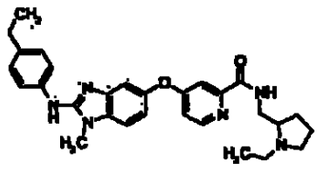
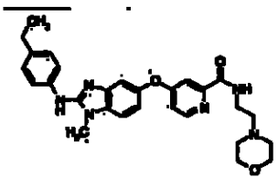
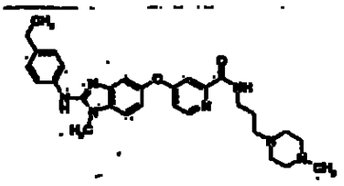
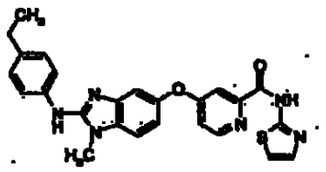
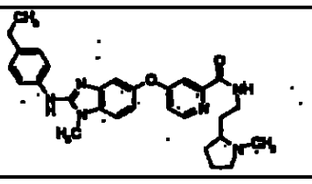
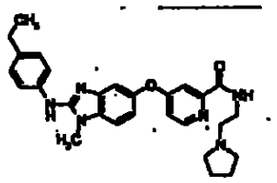
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
534		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piridin-4-iletil)-piridin-2-carboxamida	551.5	484
535		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-propilpiridin-2-carboxamida	488.5	484
536		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-pirrolidin-1-iletil)-piridin-2-carboxamida	543.5	484
537		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[(1-etilpirrolidin-2-il)metil]-piridin-2-carboxamida	568.5	485
538		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1-metil-pirrolidin-2-il)etil]-piridin-2-carboxamida	568.5	485
539		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(metiloxi)etil]-piridin-2-carboxamida	515.4	485

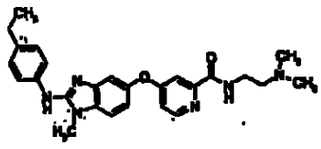
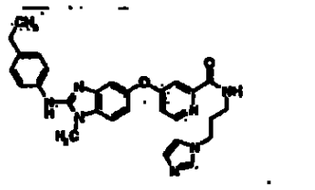
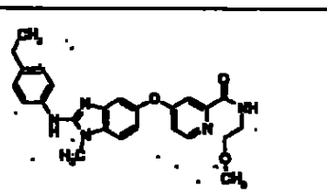
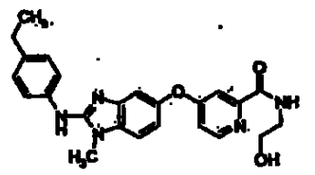
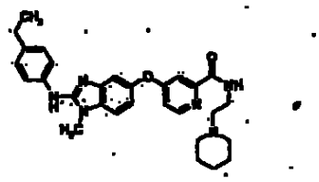
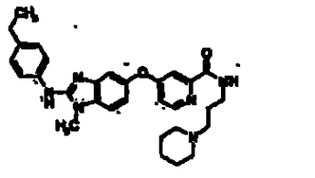
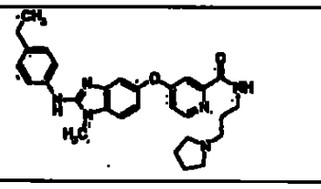
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
540		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-piperidin-1-iletil)-piridin-2-carboxamida	568.5	485
541		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-piridin-4-iletil)-piridin-2-carboxamida	562.4	485
542		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(metiloxi)-propil]-piridin-2-carboxamida	529.4	485
543		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-propilpiridin-2-carboxamida	485.3	485
544		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-etilpiridin-2-carboxamida	485.3	485
545		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[(3R)-pirrolidin-3-il]-piridin-2-carboxamida	526.4	485
546		4-({2-[(4-bromo-3-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(2-oxopirrolidin-1-il)propil]-piridin-2-carboxamida	582.4	485

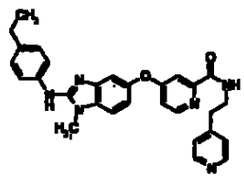
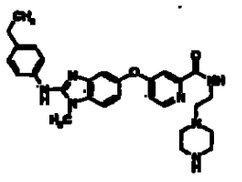
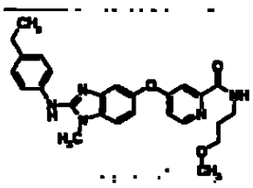
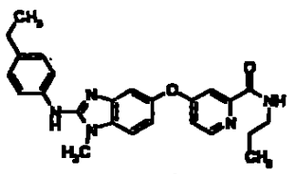
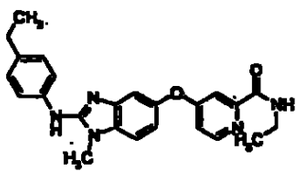
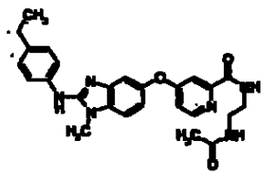
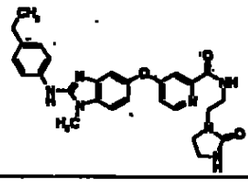
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
547		N-[(1-etilpirrolidin-2-il)-etil]-4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)pirridin-2-carboxamida	485.6	486
548		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-(2-morfolin-4-iletil)-piridin-2-carboxamida	487.6	486
549		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	514.6	486
550		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-1,3-tiazol-2-ilpiridin-2-carboxamida	457.5	486
551		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-[3-(1-metilpirrolidin-2-il)etil]-piridin-2-carboxamida	485.6	486
552		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-(2-pirrolidin-1-iletil)-piridin-2-carboxamida	571.6	486
553		N-[2-(dimetilamino)-etil]-4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)pirridin-2-carboxamida	445.5	486

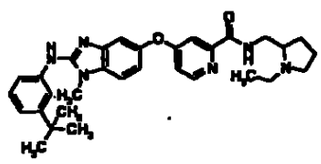
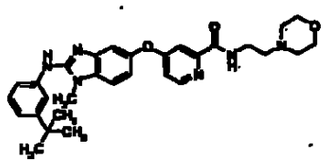
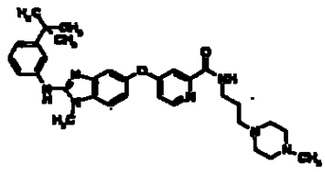
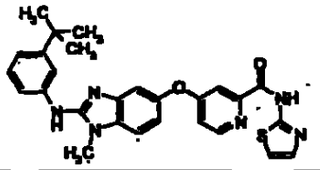
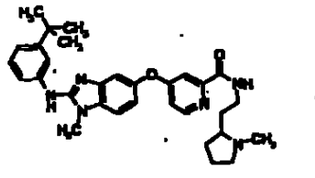
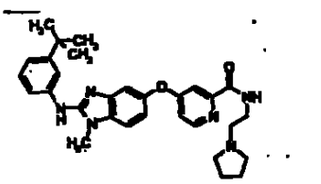
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
554		N-[3-(1H-imidazol-1-il)propil]-4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	482.6	486
555		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-[2-(metilxi)etil]-piridin-2-carboxamida	432.5	486
556		N-(2-hidroxietil)-4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	418.5	486
557		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-1,3-tiazol-2-il-piridin-2-carboxamida	457.5	486
558		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-[3-(2-oxolpirrolidin-1-il)etil]-piridin-2-carboxamida	499.6	486
559		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-(3-piperidin-1-ilpropil)-piridin-2-carboxamida	499.6	486
560		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-(3-pirrolidin-1-ilpropil)-piridin-2-carboxamida	485.6	486

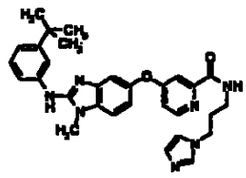
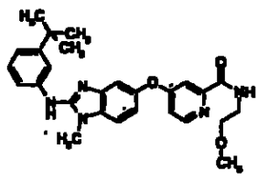
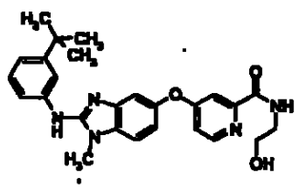
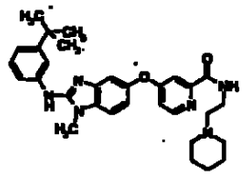
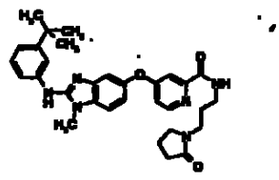
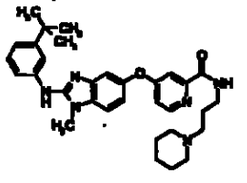
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
561		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-(2-piperidin-4-iletill)-piridin-2-carboxamida	479.6	486
562		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-(2-piperazin-iletil)-piridin-2-carboxamida	486.6	486
563		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-[3-(metiloxy)-propil]-piridin-2-carboxamida	446.5	486
564		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-propilpiridin-2-carboxamida	416.5	486
565		N-etil-4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	402.5	486
566		N-[2-(acetilamino)etil]-4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	459.5	486
560		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N-[2(2-oximidazolin-1-il)etil] piridin-2-carboxamida	486.5	486

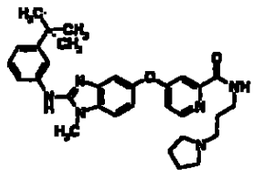
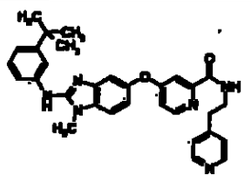
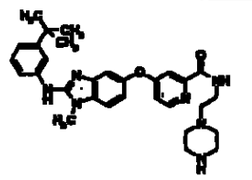
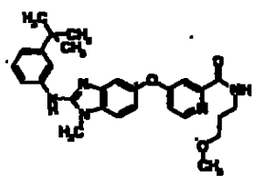
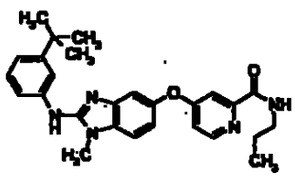
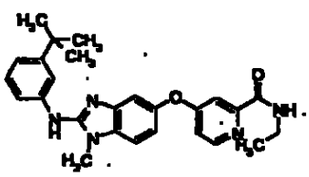
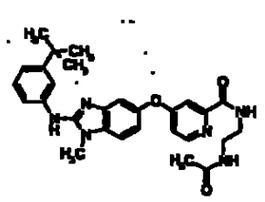
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
568		4-({1-metil-2-[(4-metilfenil)amino]-1H-bencimidazol-5-il}oxi)-N[(3R)-pirrolidin-3-il]-piridin-2-carboxamida	443.5	486
569		4-({2-[(4-etilfenil)-amino]-1-metil -1H-bencimidazol-5-il}oxi)-N-[(1-etilpirrolidin-2-il)metil]-piridin-2-carboxamida	499.6	487
570		4-({1-metil-2-[(4-etilfenil) amino] -1-metil-1H-bencimidazol -5-il}oxi] -N-(2-morfolin-4-iletil)-piridin-2-carboxamida	501.6	487
571		4-({1-metil-2-[(4-etilfenil) amino] -1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	528.7	487
572		4-({2-[(4-etilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-1,3-tiazol-2-ilpiridin-2-carboxamida	471.6	487
573		4-({2-[(4-etilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1-metilpirrolidin-2-il)etil]-piridin-2-carboxamida	499.6	487
574		4-({2-[(4-etilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N- (2-pirrolidin-1-iletil) piridin-2-carboxamida	486.5	486

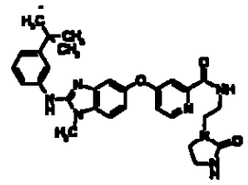
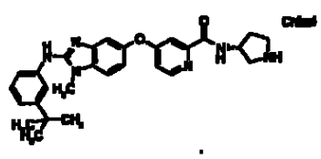
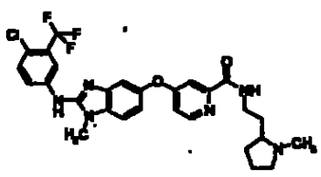
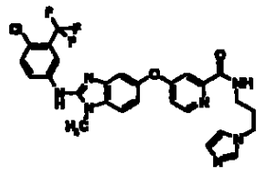
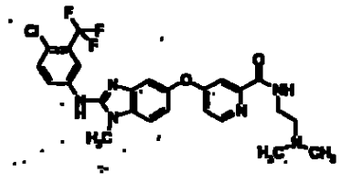
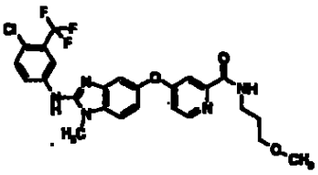
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
575		N-[2-(dimetilamino)-etil]-4-({2-[(4-etil-fenil)amino] -1-metil-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	459.6	487
576		4-({2-[(4-etilfenil)-amino]-1-metil -1H-bencimidazol-5-il] oxi-N3-(1H-imidazol-1-il)-propil] piridin-2-carboxamida	496.6	487
577		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-[2-(metiloxi) etil]-piridin-2-carboxamida	446.5	487
578		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-(2-hidroxietil) piridin-2-carboxamida	432.5	487
579		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-(2-piperidin-1-iletil) piridin-2-carboxamida	499.6	487
580		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-(3-piperidin-1-ilpropil) piridin-2-carboxamida	513.7	487
581		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-(3-pirrolidin-1-ilpropil) piridin-2-carboxamida	499.6	487

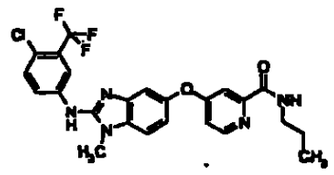
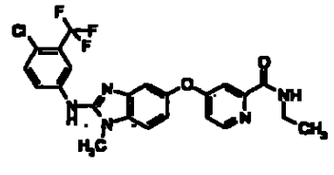
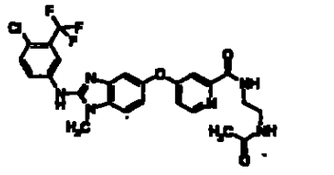
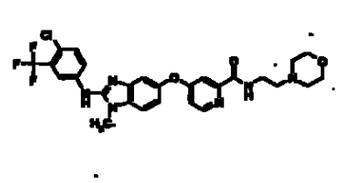
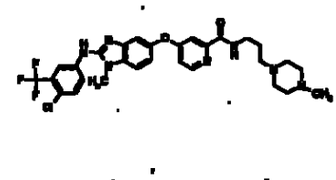
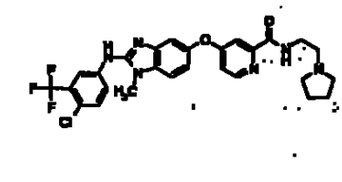
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
582		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-(2-piridin-4-iletil) piridin-2-carboxamida	493.6	487
583		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-(2-piperazin-1-iletil) piridin-2-carboxamida	500.6	487
584		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-[3-(metiloxi)propil]-piridin-2-carboxamida	460.5	487
585		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) -N-propil-piridin-2-carboxamida	430.5	487
586		N-etil-4({2-[(4-etil-fenil)amino]-1-metil-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	416.5	487
587		N-[2-(acetilamino)-etil]-4-({2-[(4-etil-fenil)amino] -1-metil-1H-bencimidazol-5-il}oxi) piridin-2-carboxamida	473.5	487
588		4-({2-[4-etilfenil)-amino] -1-metil-1H-bencimidazol -5-il}oxi) –N[2-(2-oxioimidazolidin-1-il)etil] piridin-2-carboxamida	500.6	487

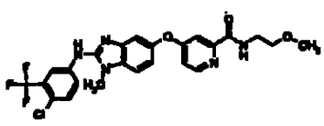
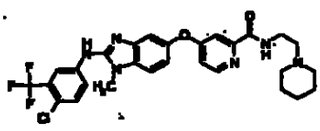
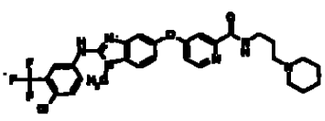
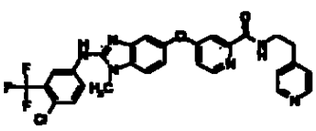
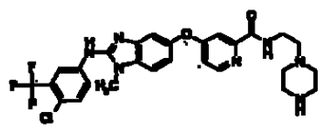
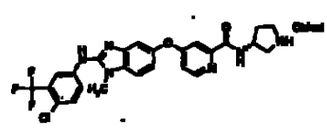
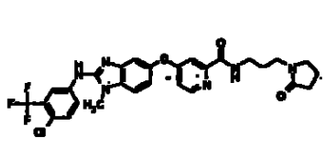
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
589		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[(1-etil-pirrolidin-2-il)metil]-piridin-2-carboxamida	527.7	488
590		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-iletil)-piridin-2-carboxamida	529.7	488
591		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	556.7	488
592		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-1,3-tiazol-2-il-piridin-2-carboxamida	499.6	488
593		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(1-metil-pirrolidin-2-il)etil]-piridin-2-carboxamida	527.7	488
594		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-pirrolidin-iletil) piridin-2-carboxamida	513.7	488

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
595		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(1H-imidazol-1-il)propil]-piridin-2-carboxamida	524.6	488
596		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(metiloxi)etil] piridin-2-carboxamida	474.6	488
597		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-hidroxietil) piridin-2-carboxamida	460.5	488
598		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperidin-1-il-etil) piridin-2-carboxamida	527.7	488
599		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(2-oxopirrolidin-1-il)propil]-piridin-2-carboxamida	541.7	488
600		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(3-piperidin-1-il-propil) piridin-2-carboxamida	541.7	488

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
601		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(3-pirrolidin-1-il-propil) piridin-2-carboxamida	527.7	488
602		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piridin-4-il-etil) piridin-2-carboxamida	521.6	488
603		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperazin-1-il-etil) piridin-2-carboxamida	528.7	488
604		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(metiloxi)propil] piridin-2-carboxamida	488.6	488
605		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-propil-piridin-2-carboxamida	458.6	488
606		4-[(2-{[3-(1,1-dimetil-etil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-etil-piridin-2-carboxamida	444.5	488
607		N-[2-(acetilamino)etil]-4-[(2-{[3-(1,1-di-metiletil)fenil]-amino}-1-metil-1H-bencimidazol -5-il)oxi]-piridin-2-carboxamida	501.6	488

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
608		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(2-oxo-imidazolidin-1-il)etil] piridin-2-carboxamida	528.6	488
609		4-[(2-{[3-(1,1-dimetil-etil)fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[(3R)-pirrolidin-3-il] piridin-2-carboxamida	485.6	489
610		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(1-metilpirrolidin-2-il)etil] piridin-2-carboxamida	574.0	489
611		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(1H-imidazol-1-il)propil] piridin-2-carboxamida	571.0	489
612		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(dimetilamino)-etil] piridin-2-carboxamida	534.0	489
613		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(metiloxi)propil] piridin-2-carboxamida	534.9	489

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
614		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-propil- piridin-2-carboxamida	504.9	489
615		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-etil- piridin-2-carboxamida	490.9	489
616		N-[2-(acetilamino)etil]-4-[(2-{[4-cloro-3(trifluorometil)-fenil]-amino}-1-metil-1H-bencimidazol -5-il)oxi]-piridin-2-carboxamida	547.9	489
617		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-il-etil) piridin-2-carboxamida	576.0	489
618		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(4-metilpiperazin-1-il] piridin-2-carboxamida	603.1	489
619		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-pirrolidin-1-iletil) piridin-2-carboxamida	560.0	489

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
620		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(metiloxi)etil] piridin-2-carboxamida	520.9	489
621		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperidin-1-iletil) piridin-2-carboxamida	574.0	489
622		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(3-piperidin-1-il-propil) piridin-2-carboxamida	588.0	489
623		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piridin-4-iletil) piridin-2-carboxamida	568.0	489
624		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperazin-1-iletil) piridin-2-carboxamida	575.0	489
625		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[(3R)-pirrolidin-3-il] piridin-2-carboxamida	531.9	489
626		4-[(2-{[4-cloro-3-(trifluorometil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(2-oxipirrolidin-1-il)propil] piridin-2-carboxamida	588.0	489

Ejemplo 627

Paso 1. Síntesis de [4-(2-{[4-(clorometil)fenil]carbonilamino}-1-metilbencimidazol-5-iloxi)(2-piridil)-N-metilcarboxamida

A una solución de tiocianato de sodio (1 eq) en acetona se agregó lentamente en una solución de 4-(clorometil)benzoilcloruro (1 eq) en acetona a 10 grados C. La mezcla fue luego filtrada a una solución de {4-[3-amino-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida (1 eq) en acetona. La formación de N-aciltioúrea fue seguida por LC/MS. La mezcla fue concentrada y sacada en tetrahidrofurano y a esto se agregó 1-etil-(3-dimetilaminopropil)carbodimidahidrocloruro (2 eq) y agitado a temperatura ambiente por 16 H. La capa orgánica fue luego secada y copncentrada para dar [4-(2-{[4-(clorometil)fenil]carbonilamino}-1-metilbencimidazol-5-iloxi)(2-piridil)-N-metilcarboxamida. MS:MH+=449.

Paso 2. Síntesis de N-metil{4-[1-metil-2({4-[(4-metilpiperazinil)metil]-fenil}carbonilamino)bencimidazol-5-iloxi](2-piridil)}carboxamida.

A la solución de [4-(2-{[4-(clorometil)fenil]carbonilamino}-1-metilbencimidazol-5-iloxi)(2-piridil)-N-metilcarboxamida (1 eq) en tetrahidrofurano se le agregó metilpiperazina (4eq) y se agitó a temperatura ambiente por 16 h. La mezcla de reacción fue concentrada y purificada sobre cromatogRafía preparativa para dar N-metil{4-[1-metil-2({4-[(4-metilpiperazinil)metil]-fenil}carbonilamino)bencimidazol-5-iloxi](2-piridil)}carboxamida. MS:MH+=512.

Ejemplo 628

Paso 1. Síntesis de N-metil[4-(1-metil-2-{2-{4-[4-metilpiperazinil]metilfenil}-benzimidazol-5-iloxi}(2-piridil))carboxamida

A la solución de {4-[3-amino-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida (1eq) en tetraidrofurano se añadió 4-(clorometil) benzoilcloruro (1eq) y trietilamina (2eq). N-acilacion fue completada en 0.5 h. La mezcla reactiva fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y el producto crudo fue adicionado con metilpiperazina (4eq) y tetraidrofurano y agitado por 16 h. a temperatura ambiente. La mezcla reactiva fue concentrada y dividida entre etil acetato y agua. La capa fue concentrada y tomada en ácido acético y calentada a 60° C por 3 h. La cromatogRafía preparativa dió N-metil{4-(1-metil-2-{2-{4-[(4-metilpiperazinil)metil-fenil}-bencimidazol-5-iloxi)(2-piridil)]carboxamida. MS: MH+ = 470.

Ejemplo 629

Paso 1. Síntesis de 2-cloro-4-(3-piridil)pirimidina.

Nitrógeno fue burbujeado a través de la solución de 2,4-dicloropirimidina (1eq) en tetrahidrofurano y agua (3:1) por 0.5 h. Bis (difenilfosfino) ferroceno cloruro de paladio (II) (0,05eq) seguido por piridina-3-ácido borónico (1eq) bicarbonato de sodio (3eq) fueron adicionados y la mezcla fue calentada a 60°C por 16 h. bajo nitrógeno. La mezcla reactiva fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue lavada con salmuera y secada con sulfato de sodio y concentrada. La purificación sobre silica gel dió 2-cloro-4-(3-piridil)pirimidina. MS: MH+ = 190.

Paso 2. Síntesis de 2-nitro-4-(4-(3-piridil)piimidin-2-iloxi)fenilamina.

Una solución de 4-amino-3-nitro-fenol (1eq) y 2-cloro-4-(3-piridil)pirimidina (1eq) en N,N-dimetilformamida fue llevada a micro-ondas a 150°C por 10 mins. La mezcla reactiva fue dividida entre cetato de etiol y agua. La capa orgánica fue concentrada y purificada en silica gel para dar 2-nitro-4-(4-(3-piridil)pirimidina-2-iloxi)penilamina. MS: MH+ = 309.

Paso 3. Síntesis de 4-(4-(3-piridil)pirimidina -2-iloxi)benceno-1,2-diamine

La mezcla que contiene 2-nitro-4-(4-(3-piridil)pirimidina-2-iloxi)fenilamina en metanol con cantidad catalítica de 10% Pd/C fue hidrogenada hasta que desapareció el color amarillo para dar 4-(4-(3-piridil)pirimidina-2-iloxi)fenilamina. MS:MH+ = 279.

Paso 3. Síntesis de {4-[(4-metilpiperazinil)metil]fenil}-N-{5-(4-(3-piridil)-pirimidina-2-iloxi)bencimidazol-2-il]carboxamida.

Una solución de tiocianato de sodio (1eq) en acetona fue añadida lentamente en la solución de 4-(clorometil)benzoilcloruro (1eq) en acetona a 0°C. La mezcla fue filtrada en la solucion de 4-(4-(3-piridil)pirimidina-2-iloxi)benceno-1,2-diamina (1eq) en acetona. La formación de N-aciltioúrea fue seguida por LC/MS. La mezcla fue concentrada y tomada en tetrahidrofurano y fue adicionado 1-etil-(3-dimetilaminopropil)carbodimidahidrocloruro (2eq) y agitada a temperatura ambiente por 16 h. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue secada y concentrada para dar [4-(clorometil)fenil]-N-[5-(4-(3-piridil)pirimidina-2-iloxi)bencemidazol-2-il-]carboxamida. Fue tomada en tetrahidro-furano y adicionado metilpiperazina (4eq) y agitada a temperatura ambiente por 16 h. La mezcla reactiva fue concentrada y purificada en cromatogRafía preparativa para dar {4-[(4-metilpiperazinil)metil]fenil}-N-{5-(4-(3-piridil)pirimidina-2-iloxi)bencemidazol-2-il]-carboxamida. MS. MH+ = 520.

Ejemplo 630

Paso 1. Síntesis de 4-etil-1-[(4-nitrofenil)metilpiperazina

A 4-(clorometil)-1-nitrobenceno (1eq) en tetrahidrofurano se le adicionó etilpiperazina (3eq) y fue agitada por 16 h a temperatura ambiente. Concentrado y filtrado a través de una capa de silica dió 4-etil-1-[(4-nitrofenil)metilpiperazina]. MS: MH+ =249.

Paso 2. Síntesis de 4-[(4-etilpiperazinil)metil]fenilamina

La mezcla que contiene 4-etil-1-[(nitrofenil)metilpiperazina en metanol con cantidad catalítica del 10% Pd/C fue hidrogenada para dar 4-[(4-etil-piperazinil)metil]fenilamina. MS: MH+ =219.

Paso 3 . Síntesis de 4-[(4-etilpiperazinil)metil]bencenisotiocianato.

A 4-[(4-etilpiperazinil)metil]fenilamina en acetona a 0°C se le adicionó bicarbonato de sodio (2eq) y tiosfogeno (2eq). La mezcla fue agitada a temperatura ambiente, concentrada y dividida entre etil acetato y agua. La capa orgánica fue secada con bicarbonato de sodio y sulfato de sodio y concentrada para dar 4-{(4-etilpiperazinil)metil}bencenisoticinanto. MS:MH+ = 261.

Paso 4. Síntesis de [4-[(2-{[4-etilpiperazinil)metil]fenil]amino)-1-metilbencimidazol-5-iloxi)(2-piridil)]-N-metilcarboxamida.

Al 4-[(etilpiperazinil)metil]bencenoisotiocinanto (1eq) en metanol fue agregado {4-[3-amino-4-(metilamino)fenoxil](2-piridil)}-N-metilcarboxamida (1eq) y calentada a 60°C por 16h. CromatogRafía preparativa dió {4-[(2-{(4-etilpiperazinil)metil}fenil)amino]-1-metilbencimidasol-5-iloxi}(2-piridil)-N-metilcarboxamide. MS: MH+ = 499.

Ejemplo 631

Paso 1. Síntesis de 4-etil-1-(4-nitrofenil)piperazina

A 4-fluoro-1-nitrobenceno(1eq) en N,N-dimetilformamida fue agregada etilpiperazina (2eq) y N,N-diisopropiletil amina (2eq) y calentada a 80°C por 16 h. La mezcla reactiva fue dividida entre etil acetato y agua . La capa orgánica fue entonces lavada con la salmuera y secada con sulfato de sodio y concentrada. Luego se pasó a través de una capa de silica para dar 4-etil-1-(4-nitrofenil)piperazina. MS: MH+ = 235.

Paso 2. Síntesis de 4-(4-etilpiperazinil)fenilamina

La mezcla que contiene 4-etil-1-(4-nitrofenil)piperazina en metanol con la cantidad catalítica de 10% Pd/C fue hidrogenada para dar 4-(4-etilpiperazinil)fenil-amina. MS: MH+ = 205.

Paso 3. Síntesis de 4-(4-etilpiperazinil)bencenoisotiocianato.

A 4-(4-etilpiperazinil)fenilamina en acetona a 0°C fue agregado bicarbonato de sodio (2eq) y tiofosgeno (2eq). La mezcla fue llevada a temperatura ambiente, concentrada y dividida entre etil acetato y agua. La capa orgánica fue secada con bicarbonato de sodio y sulfato de sodio y concentrada para dar 4-(4-etilpiperazinil)bencenoisotiocianato. MS: MH+ = 247.

Paso 4. Síntesis de [4-(2-{[4-etilpiperazinil)fenil[amina)-1-metil-bencimidazol-5-iloxi)(2-piridil)]-N-metilcarboxamida.

A 4-(4-etilpiperazinil)bencenoisotiocianato (1eq) en metanol fue añadido {4-[-3-amino-4-(metilamino)fenoxi]-(2-piridil)}-N-metilcarboxamida (1eq) y calentado a 60°C por 16h. La purificación preparativa dió [4-(2-({[4-etilpiperazinil]fenil}-amino)-1-metil-bencimedazol-5-iloxi)(2-piridil)]-N-metilcarboxamida. MS: MH+ = 485.

Ejemplo 632

Paso 1. Síntesis de 4-(2-bromoetil)-1-nitrobenceno

A 4-(2-bromoetil)-1-nitrobenceno (1eq) en tetrahidrofurano fue agregado morfolina (3eq) y fue agitado por 16 h. a temperatura ambiente. Concentrándolo y pasándolo a través de un a capa de sílica dió 4-[2-(4-nitrofenil)etilmorfolina. MS:MH+ = 236.

Paso 2. Síntesis de 4-(2-morfolina-4-iletil)fenilamina

La mezcla que contiene 4-[2-(4-nitrofenil)etil]morfolina en metanol con la cantidad catalítica de 10% Pd/C fue hidrogenada para dar 4-(2-morfolina-4-iletil)fenilamina. MS. MH+ = 206.

Paso 3. Síntesis de 4-(2-morfolina-4-iletil)bencenisotiocianato.

A 4-(2-morfolina-4-iletil)fenilamina en acetona a 0°C fue agregado bicarbonato de sodio (2eq) y tiosfogeno (2eq). La mezcla fue llevada a temperatura ambiente, concentrada y dividida entre etil acetato y agua. La capa orgánica fue secada con bicarbonato de sodio, sulfato de sodio y concentrada para dar 4(2-morfolina-4-iletil)bencenisotiocianato. MS: MH+ = 252.

Paso 4. Síntesis de N-metil[4-(1-metil-2-{[4-(2-morfolina-4-iletil)fenil]amino}-bencimidazol-5-oxi)(2-piridil)]carboxamida.

A 4(2-morfolina-4-iletil)bencenisotiocianato (1eq) en metanol fue agregado {4-[3-amina-4-(metilamina)fenoxi](2-piridil)}-N-metilcarboxamida (1eq) y agitado a temperatura ambiente por 16 h. La formación de la tioúrea correspondiente fue seguida por LC/MS. A esto se le añadió iodometano (1eq) y calentado a 60°C por 3 h. La concentración seguida por cromatogRafía preparativa dió N-metil[4-(1-metil-2-{[4-(2-morfolina-4-iletil)fenil]amina}-bencimidazol -5-oxi)(2-piridil)]carboxamida. MS: MH+ = 486.

Ejemplo 633

Paso 1. Síntesis de [(4-nitrofenil)etil]bencilamina

A una solución de 1-(4-nitrofenil)etano-1-ona (1eq) y fenilmetilamina (1eq) en metanol fue agregado sodiotriacetoxiborohidruro (1.2eq). La mezcla resultante fue agitada a temperatura ambiente por 16 h. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y la purificación preparativa dió [(4-nitrofenil)etil]bencilamina. MS: MH+ = 256.

Paso 2. Síntesis de [(4-aminofenil)etil]bencilamina

La mezcla que contiene [(4-nitrofenil)etil]bencilamina en metanol con la cantidad catalítica de 10% Pd/C fue hidrogenada hasta que desapareció el color amarillo del producto [(4-aminafenil)etil]bencilamina. MS: MH+ = 226.

Paso 3. Síntesis de 4-{[bencilamina]etil}bencenoisotiocianato.

A [(4-nitrofenil)etil]bencilamina en acetona a 0°C fue agregado bicarbonato de sodio (2eq) y tiofosgeno (2eq). La mezcla fue llevada a temperatura ambiente, concentrada y dividida entre etil acetato y agua. La capa orgánica fue secada con bicarbonato de sodio, sulfato de sodio y concentrada dió 4-{[bencilamino]etil}bencenoisotiocianato. MS: MH+ = 268.

Paso 4. Síntesis de N-metil(4-{1-metil-2-2{(4-{[bencilamino]etil}-fenil)amino)-bencimidazol-5-iloxi)-(2-piridil))carboxamida.

A la solución de [4-(3,4-diaminofenoxi)(2-piridil))]-N-metilcarboxamida (1eq) en metanol fue agregado 4-{{bencilamino]etil}bencenisotiocianato (1eq) y calentado a 60°C por 3h. La cromatogafia preparativa dió N-metil(4-{1-metil-2-2-[(4-{[bencilamino]-etil}fenil)amino) bencimedazol-5-iloxi)-(2-piridil))-carboxamida. MS: MH+ = 506.

Ejemplo 634

Paso 1. Síntesis de (5-fluoro-2-nitrofenil)metilamina

Una solución de 5-fluoro-2-nitrofenilamina (1eq) en cloruro de metileno fue tratada con anhídrido trifluoroacético (1eq) y agitado por 10 minutos a 0°C. La mezcla fue apagada con la solución de bicarbonato de sodio saturado. La capa orgánica fue separada y lavada con agua y salmuera, secada y evaporada. A la solución de trifluoroacetamida (1eq) en la mezcla de tolueno, acetonitrilo y solución de hidróxido de sodio (50%) fue agregado cloruro de benciltrimetilamonio (1eq) y dimetilsulfato (1.2eq). La mezcla bifásica fue agitada toda la noche a temperatura ambiente y evaporada. La mezcla fue tomada en etil acetato, lavada con

agua salmuera, secada y evaporada. El crudo fue purificado pór cromatogRafía de columna cargada con 1:1 hexanos y etil acetato para dar (5-fluoro-2-nitrofenil)metilamina. MS: MH+ = 170.

Paso 2. Síntesis de {4-[4-amino-3-(metilamino)fenoxi](2-piridil)}-N-metil-carboxamida.

La mezcla que contiene 5-fluoro-2-nitrofenilamina (1eq), potasio bis(trimetilsilil)amida (2eq) fue agitada en dimetilformamida por 2 h. a temperatura ambiente. A la mezcla fue agregada (3-hidroxifenil)-N-metilcarboxamida (1eq) y carbonato de potasio (1.2eq) y agitado a 90°C por 16 h. La mezcla reactiva fue concentrada y dividida entre etil acetato y agua. La capa orgánica fu separada y lavada con salmuera, secada, filtrada y concentrada en vacío para dar un sólido castaño. Purificación en silica gel dió N-metil{4-[3-(metilamino)4-nitro-fenoxy](2-piridil))carboxamida. Fue tomada en metanol e hidrogenada con cantidad catalítica de 10% Pd/C para dar {4-[4amino-3(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida. MS: MH+ = 272.

Paso 3. Síntesis de (4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-6-iloxi)-(2-piridil)-N-metilcarboxamida.

Una solución de {4-[4-amino-3-(metilamino)fenoxi](2-piridil)-N-metil-carboxamida (1eq) en metanol fue tratada con 4-bromofenilisotiocianante (1eq) y agitada a 60°C por 2 h. La mezcla de reacción fue enfriada a temperatura ambiente e iodometano (1eq) fue agregado y agitado durante la noche a 60°C. La reacción fue concentrada y la cromatogRafia preparativa dio como resultado (4-{2-[(4-bromofenil)amino]-1-metilbencimidazol-6-iloxi)-(2-piridil)-N-metil-carboxamida. MS: MH+ = 452.

Ejemplo 635

Paso 1. Síntesis de ((5-aminobencimidazol-2-il)(4-bromofenilamina)

Una solución de 4-nitrobenceno-1,2- diamino en metanol fue tratada con 4-bromofenil isotiocianato (1eq) y agitada a 60°C por 2 h. La mezcla reactiva fue enfriada a temperatura ambiente y iodometano (1eq) fue agregado y agitado durante la noche a 60°C . La reacción fue concentrada y purificada con silica gel para dar (4-bromofenil)5-nitrobencimidazol-2-il)amina. El producto fue tomado en metanol e hidrogenado con cantidad catalítica de 10%Pd/C para dar ((5-aminobenzimidazol-2-il)(4-bromofenilamina). MS: MH+ = 302.

Paso 2 Síntesis de 4-({2-[(4-bromofenil)amino]bencimidazol-5-il}amino)-(2-piridil)-N-metilcarboxamida.

A una solución de ((5-aminobencimidazol-2-il)(4-bromofenilamino(1eq) en N,N-dimetilformamida fue agregado hidruro de sodio (2eq) y la mezcla fue llevada a microondas por 8 mins a 220°C. La mezcla reactiva fue dividida entre etil acetato y agua y la capa orgánica fue secada con sulfato de sodio concentrada. CromatogRafía preparativa dió [4-({2-[(4-bromofenil)amino}becimidazol-5-il}amino)(2-piridil)_-N-metilcarboxamida. MS: MH+ = 437.

Ejemplo 636

Paso 1. Síntesis de (4-{2-[(4-bromofenil)metil]-1-metilbencimidazol-5-iloxi)-(2-piridil))-N-metilcarboxamida.

A 4-bromofenil ácido acético (1eq) en diclorometano conteniendo una gota de N,N-dimetilformamida a 0°C fue agregado oxalil cloruro (1.2eq). La mezcla resultante fue llevada a temperatura ambiente y agitada por 2 h. La mezcla fue concentrada y le añadió tetrahidrofuran y [4-(3,4-diaminafenoxi)(2-piridil)]-N-metilcarboxamida (1eq) y trietilamina (1eq) y agitada por 2 h. La formación del producto N-acilado fue seguido por LC/MS. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue secada con sulfato de sodio y concentrada y tomada en ácido acético y calentada a 60°C por 2 h. La

cromatogRafia preparativa dió (4-{2-[(4-bromofenil)metil]-1-metilbencimidazol-5-iloxi)-(2-piridil))-N-metilcarboxamida. MS: MH+ =451.

Ejemplo 637

Paso 1. Síntesis de 4-({1-metil-5-[2-(N-metilcarbamoil)(4-piridil-oxi))] bencimidazol-2-il}amino) ácido benzoico

A {4-[3-amino-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida (1eq) en metanol fue añadido ácido 4-isotiocianatobenzoico (1eq) y agitado a 60°C por 3 h. Entonces a esto le fue añadido iodometano (1eq) y calentado a 60°C por 3 h. Concentrado el solvente y purificado sobre silica gel para dar.como resultado 4-({1-metil-5-[2-(N-metilcarbamoil)(4-piridil-oxi))]bencimidazol-2-il}amino) ácido benzoico. MS: MH+ =417.

Paso 2. Síntesis de N-metil[4-(1-metil-2-{[4-(2-morfolina-4-iletil)fenil]-amino-bencimidazol-5-oxi)(2-piridil)]carboxamida CHIR-164277

A 4-({1-metil-5-[2-(N-metilcarbamoil)(4-piridiloxi))]bencimidazol-2-il}-amino) ácido benzoico (1eq) en tetrahidrofurano fue añadido morfolina (2eq) y N,N-diisopropiletilamina(4eq) y HBTU(2eq) y agitado a temperatura ambiente por 16 h.

La mezcla fue entonces concentrada y dividida entre acetato de etil y agua. La capa orgánica fue lavada con salmuera y secada con sulfato de sodio. La cromatogRafía preparativa dio como resultado N-metil[4-(1-metil-2-{[4-(2-morfolino-4-iletil)fenil]-amino-bencimidazol-5-oxi)(2-piridil)]carboxamida. MS: MH+ =529.

Ejemplo 638

Paso 1. Síntesis de 3-({1-metil-5-[2-(N-metilcarbamoil)(4-piridiloxi))]-bencimidazol-2-il}amino) ácido benzoico

A 4-[3-amino-4- (metilamino) fenoxi](2-piridil)}-N-metilcarboxamida (1eq) en metanol fue añadido 3-isotiocianatobenzoico (1eq) y agitado a 60°C por 3 h. A esto le fue

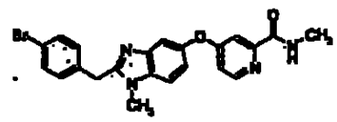
añadido iodometano (1eq) y calentado a 60°C por 3 h. y concentrado el solvente y purificado sobre silica gel dió 3-({1-metil-5-[2-(N-metilcarbamoil)(4-piridiloxi))]bencimidazol-2-il}amino) ácido benzoico. MS: MH+ =417.

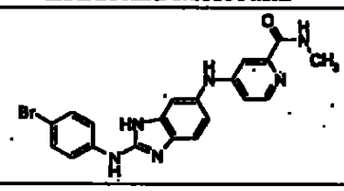
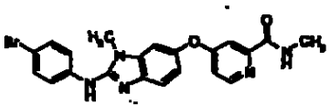
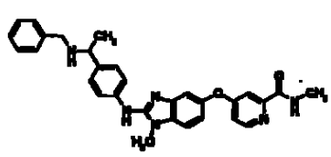
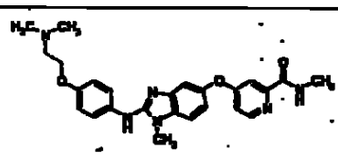
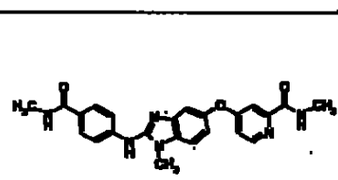
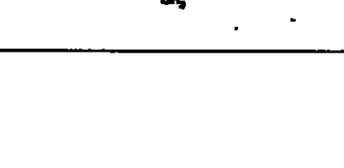
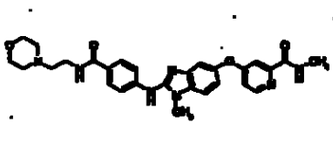
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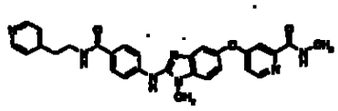
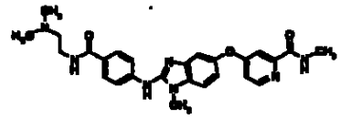
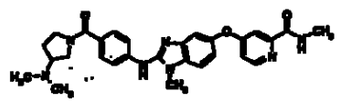
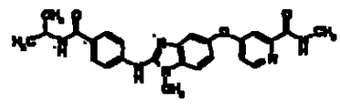
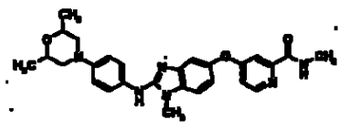
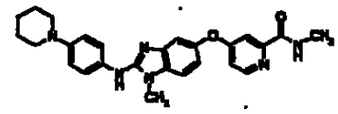
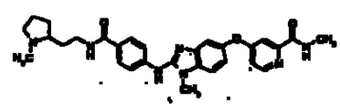
A 3-({1-metil-5-[-2(N-metilcarbamoil)(4-piridiloxi)]bencimidazol-2-il}-amino) ácido benzoico (1eq) en tetrahidrofurano le fue añadido morfolino (2eq) y N,N-diisopropiletilamina (4eq), EDCI(2eq), HOAT (1.2eq) y agitado a temperatura ambiente por16 h. La mezcla fue entonces concentrada y dividida entre acetato de etil y agua. La capa orgánica fue lavada con salmuera y secada con sulfato de sodio. La cromatogRafía preparativa dió el producto N-metil[3-(1-metil-2-{[4-(2-morfolino-4-iletil)fenil]-amino-bencimidazol-5-oxi)(2-piridil)]-carboxamida MS: MH +=529

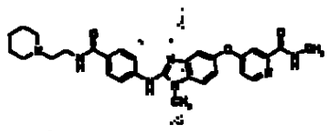
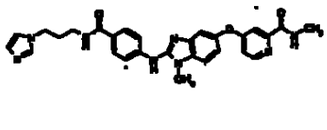
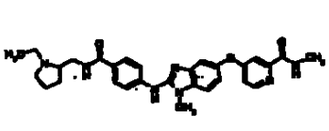
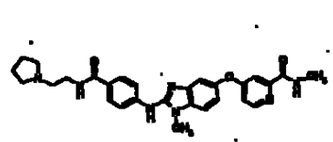
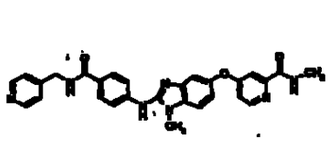
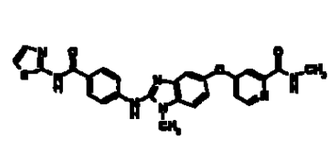
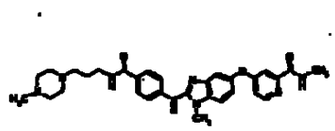
Cada uno de los compuestos 639-698, listados en la tabla 7 fueron sintetizados como fue indicado en la columna de la derecha por el método descrito en uno de los ejemplos 627-638 o de otra forma indicada.

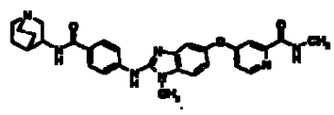
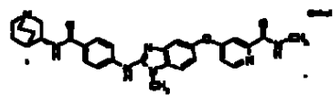
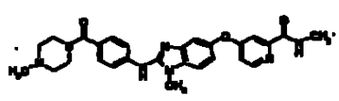
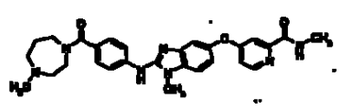
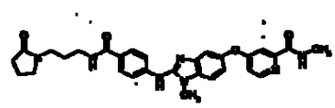
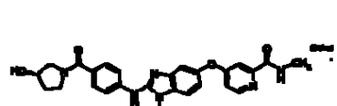
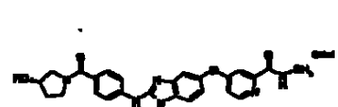
Tabla 7

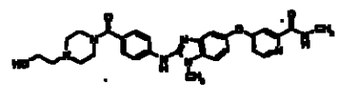
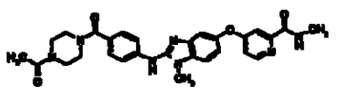
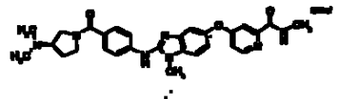
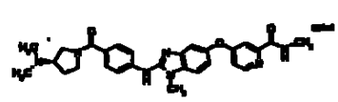
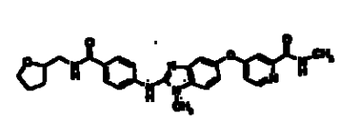
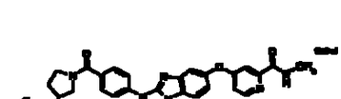
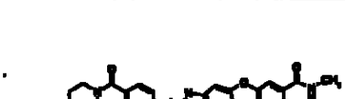
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
639		4-({2-[(4-bromofenil)metil]-1-metil-1H-bencimidazol-5-il}amino)-N-metilpiridin-2-carboximida	452.3	635

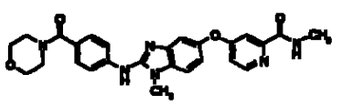
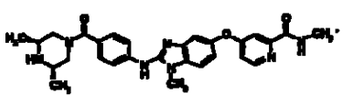
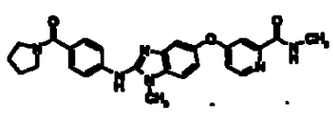
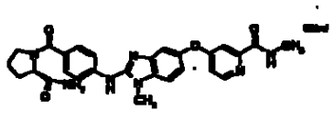
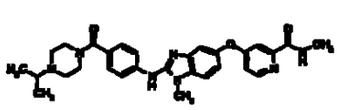
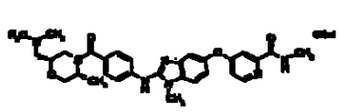
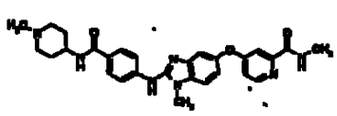
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
640		4-({2-[(4-bromofenil)-amino]-1H-bencimidazol-6-il}amino)-N-metilpiridin-2-carboximida	438.3	635
641		4-({2-[(4-bromofenil)-amino]-1-metil-1H-bencimidazol-6-il}oxi-N-metilpiridin-2-carboxamida	453.3	634
642		N-metil-4-({1-metil-2-[(4-{-[(fenilmetil)-amino]etil}fenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboximida	507.6	633
643		4-({2-[(4-{[2-(dimetil-amino)etil]oxi}fenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboximida	461.5	631
644		N-metil-4-{[1-metil-2-({4-[-[(metilamino)-carbonil]fenil}amino)-1H-bencimidazol-5-il}oxi)-piridin-2-carboximida	431.5	637
645		N-metil-4-({1-metil-2-[(4-{-[(2-morfolin-4-il-etil)amino]carbonil}fenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboximida	530.6	637
646		4-{[2-({4-[(4-etilpiperazin-1-il)carbonil]fenil}-amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carbox-amida	514.6	637

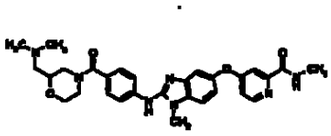
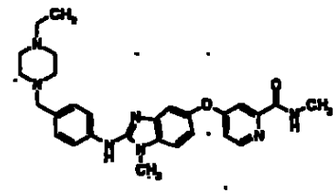
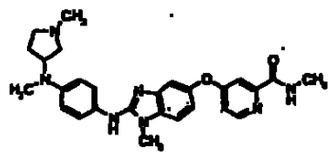
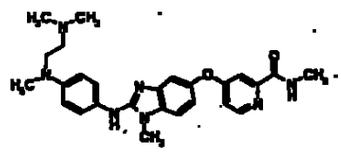
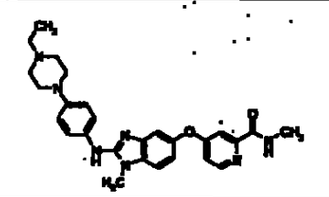
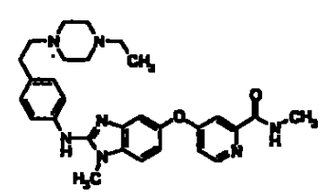
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
647		N-metil-4-({1-metil-2-[(4-{[(2-piridin-4-iletil)-amino]carbonil} fenil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	522.6	637
648		4-[(2-{[4-({[2-(dimetil-amino)etil]amino}-carbonil) fenil] amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	488.6	637
649		4-({2-[(4-{[3-(dimetil-amino (pirrolidin-1-il]-carbonil} fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	514.6	637
650		N-metil-4({1-metil-2-[(4-{[(1-metiletil)amino]-carbonil} fenil) amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	459.5	637
651		4-[(2-{[4-(2,6-dimetil-morfolin-4-il)fenil]-amino}-1-metil- 1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	487.6	120a
652		N-metil-4({1-metil-2-[(4-piperidin-1-ilfenil)-amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	457.5	120a
653		N-metil-4-[(1-metil-2-{[4-({[2-(1-metilpirrolidin-2-il)etil] amino} carbonil) -fenil] amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	528.6	637

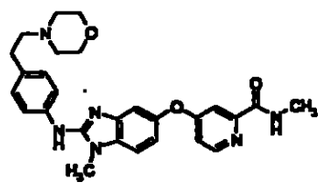
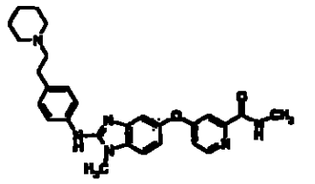
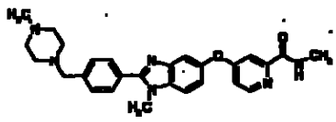
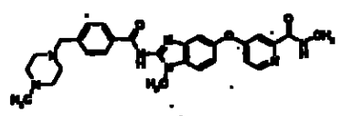
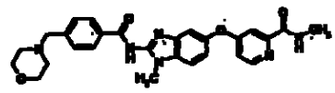
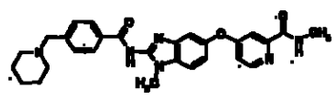
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
654		N-metil-4-({1-metil-2-[(4-{[(2-piperidin-1-iletil)amino} carbonil} fenil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	528.6	637
655		4-[(2-{[4-({[3-(1H-imidazol-1-il) propil]-amino}cabonil)-fenil] amino)-1-metil- 1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	525.6	637
656		4-[(2-{[4-({[1-etil-pirrolidin-2-il)metil]-amino}carbonil)fenil]-amino}-1-metil- 1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	528.6	637
657		N-metil-4-({1-metil-2-[(4-{[(2-pirrolidin-1-iletil)amino} carbonil} fenil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	514.6	637
658		N-metil-4-({1-metil-2-[(4-{[(piridin-4-ilmetil)amino] carbonil} fenil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	508.6	120a
659		N-metil-4{[1-metil-2-({4-[(1,3-tiazol-2-il-amino)carbonil]fenil} amino)-1H-bencimidazol-5-il]-oxi}piridin-2-carboxamida	500.6	637
660		N-metil-4-[(1-metil-2-{[4-({[3-(4-metilpiperazin-1-il)propil] amino}carbonil)-fenil]amino}-1H - bencimidazol-5-il)oxi]-piridin-2-carboxamida	557.7	637

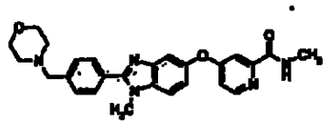
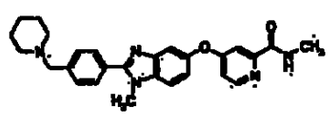
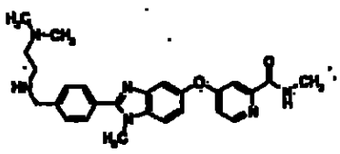
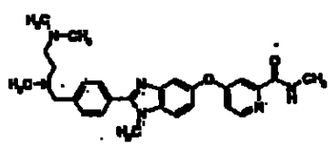
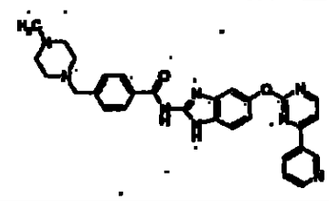
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
661		4-{[2-({4-[(1-aza-biciclo [2.2.2] oct-3-ilamino)-carbonil]fenil} amino)-1-metil-1H-bencimidazol -5-il]oxi}-N-metilpiridin-2-carboxamida	526.6	637
662		4-({2-[(4-{[(3S)-1-aza-biciclo [2.2.2] oct-3-ilamino]-carbonil} fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-matilpiridin-2-carboxamida	526.6	637
663		N-metil-4{[1-metil-2-({4-[(4-metilpiperazin-1-il) carbonil] fenil} amino)-1H-bencimidazol-5-il]-oxi}piridin-2-carboxamida	500.6	637
664		N-metil-4{[1-metil-2-({4-[(4-metil-1,4-diazepan-1-il) carbonil] fenil} amino)-1H-bencimidazol-5-il]-oxi}piridin-2-carboxamida	514.6	637
665		N-metil-4[(1-metil-2-{[4-({[3-(2-oxopirrolidin-1-il) propil] amino} carbonil) fenil] amino}-1H-bencimidazol-5-il)-oxi] piridin-2-carboxamida	542.6	637
666		4-({-2[(4-{[(3R)-3-hidroxi-pirrolidin-1-il]carbonil}-fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	487.5	637
667		4-({-2[(4-{[(3S)-3-hidroxi-pirrolidin-1-il]carbonil}-fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	487.5	637

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
668		4-({-2[(4-{[4-(2-hidroxi-etil) piperazin-1-il]-carbonil}-fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	530.6	637
669		4-{[-2{(4-[(4-acetilpiperazin-1-il)-carbonil]-fenil} –amino)-1-metil-1H-bencimidazol -5-il] oxi} -N-metilpiridin-2-carboxamida	528.6	637
670		4-({2-[(4-{[4-(2-[(4-{[(3R)-3-(dimetil-amino)pirrolidin-1-il]-carbonil}-fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	514.6	637
671		4-({2-[(4-{[4-(2-[(4-{[(3S)-3-(dimetil-amino)pirrolidin-1-il]-carbonil}-fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	514.6	637
672		N-metil-4-({1-metil-2-[(4-{[(tetrahidrofuran-2-ilmetil) amino] carbonil} fenil)amino]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	501.6	637
673		4-({2-[(4-{[4-(2-[(4-{[(3R)-3-(acetil-amino)pirrolidin-1-il]-carbonil}-fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	528.6	637
674		4-[(2-{[4-(1,4'-Bipiperidin-1'-il-carbonil)-fenil] amino}-1-metil-1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	568.7	637

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
675		N-metil-4-[(1-metil-2-{[4-(morfolin-4-il-carbonil)fenil] amino-1H-bencimidazol-5-il)-oxi] piridin-2-carboxamida	487.5	637
676		4-({-2[(4-{[(3R,5S)-3,5-dimetilpiperazin-1-il]carbonil}-fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	514.6	637
677		N-metil-4.[(1-metil-2-{[4-(pirrolidin-1-il-carbonil)fenil] amino-1H-bencimidazol-5-il)-oxi] piridin-2-carboxamida	471.5	637
678		4-({-2[(4-{[(2R)-2-(amino-carbonil)pirrolidin-1-il] carbonil} -fenil) amino]-1-metil-1H-bencimidazol -5-il}oxi)-N-metilpiridin-2-carboxamida	514.6	637
679		N-metil-4-({1-metil-2-[(4-{[4-(1-metiletil)-piperazin-1-il] carbonil}fenil) amino]-1H-bencimidazol-5-il}-oxi) piridin-2-carboxamida	528.6	637
680		4-[(2-{[4-([(2R,5S)-2-[(dimetilamino)metil]-5-metilformolin-4-il}-carbonil)-fenil] amino}-1-metil-1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	558.7	637
681		N-metil-4-({1-metil-2-[(4-{[(1-metilpiridin-4-il)amino] carbonil}fenil) amino]-1H-bencimidazol-5-il}-oxi) piridin-2-carboxamida	514.6	637

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
682		4-[(2-{[4-({2-[(dimetilamino) metil]morfolin-4-il}-carbonil)-fenil] amino}-1-metil-1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	544.6	637
683		4-{[2-({4-[(4-etilpiperazin-1-il)metil]fenil}amino)-1-metil-1H-bencimidazol-5-il]oxi)-N-metilpiridin-2-carboxamida	500.6	630
684		N-metil-4-{[1-metil-2-({4-[metil (1-metil-pirrolidin-3-il)amino]-fenil}amino)-1H-bencimidazol-5-il]-oxi} piridin-2-carboxamida	486.6	631
685		4-{[2-({4-[[2-(dimetil-amino) etil] (metil)amino]-fenil}amino)-1-metil-1H-bencimidazol-5-il] oxi)-N-metilpiridin-2-carboxamida	474.6	631
686		4-[(2-{[4-(4-etilpiperazin-1-il)fenil] amino}-1-metil-1H-bencimidazol -5-il)oxi]-N-metilpiridin-2-carboxamida	486.6	631
687		4-{[2-({4-[2-(4-etil-piperazin-1-il) etil] fenil}amino)-1.metil-1H-bencimidazol-5-il] oxi)-N-metilpiridin-2-carboxamida	514.6	632

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
688		N-metil-4-[(1-metil-2-{[4-(2-morfolin-4-iletil) fenil]amino]-1H-bencimidazol-5-il)-oxi] piridin-2-carboxamida	487.6	632
689		N-metil-4-[(1-metil-2-{[4-(2-piperidin-1-iletil) fenil]amino]-1H-bencimidazol-5-il)-oxi] piridin-2-carboxamida	485.6	632
690		N-metil-4-[(1-metil-2-{[4-(4-metilpiperazin-1-il) metil] fenil}-1H-bencimidazol-5-il)-oxi] piridin-2-carboxamida	471.6	628
691		N-metil-4-({1-metil-2-[({4-[(4-metilpiperazin-1-il) metil] fenil}-carbonil)amino]-1H-bencimidazol -5-il}-oxi) piridin-2-carboxamida	514.6	627
692		N-metil-4-{[1-metil-2-({[4-(4-morfolin-4-ilmetil) . fenil] carbonil} amino)-1H-bencimidazol -5-il]-oxi} piridin-2-carboxamida	501.6	627
693		N-metil-4-{[1-metil-2-({[4-(4-piperidin-1-ilmetil) . fenil] carbonil} amino)-1H-bencimidazol -5-il]-oxi} piridin-2-carboxamida	499.6	627

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
694		N-metil-4-({1-metil-2-[4-(morfolin-4-ilmetil)fenil]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	458.5	628
695		N-metil-4-({1-metil-2-[4-(piperidin-1-ilmetil)fenil]-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	456.6	628
696		4-({2-[4-({[2-(dimetilamino)etil]amino}metil)fenil]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	459.6	628
697		4-{[2-[4-{[(2-(dimetilamino)etil](metil)amino]metil}fenil)-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	473.3	628
698		4-[(metilpiperazin-1-il)metil]-N-{5-[(4-piridin-3-ilpirimidil-2-il)oxi]-1H-bencimidazol-2-il}benzamida	521.6	629

Ejemplo 699

Paso 1. Síntesis de {4-[2-metoxi-4-(metilamino)-5-nitrofenoxi](2-piridin)}-N-metilcarboxamida.

A una solución agitada de ácido nítrico concentrado (22 eq) fue agregado 2h-benzo[d]1,3-dioxolano (1 eq) de 0-10° C por 0.5h y agitado por otras 0.5h. A esta mexcla de reacción fue agregado ácido sulfúrico concentrado (0.06 eq) gota por gota a 0-10° C por 0.5h y

agitado a 20° C por 0.5h. Luego fue vertido sobre hielo triturado y el sólido separado fue filtrado, lavado con agua y secado para dar 5,6-dinitro-2h-benzol[d]1,3-dioxalan. MS: MH+ 212.

Paso 2. Síntesis de metil(6-nitro(2h-benzo[3,4-d]1,3-dioxalan-5-il)-amina.

A una solución agitada de metilamina en eter y etanol (1.5:1) se agregó 5,6-dinitro-2h-benzol[d]1,3-dioxalano y se agitó a temperatura ambiente por 24h. El solvente fue evaporado a vacío y el sólido fue lavado con agua y secado para dar metil(6-nitro(2h-benzo[3,4-d]1,3-dioxalan-5-il)amina.MS: MH+ 196.

Paso 3. Síntesis de 2-metoxi-4(metilamino)-5-nitrofenol.

A una solución agitada de metanol se le agregó sodio metálico (4.8 eq) lentamente a temperatura ambiente, seguido por metil(6-nitro(2h-benzo[3,4-d]1,3-dioxalan-5-il)amina (1 eq) y agitado por 2h. La mezcla fue entonces reflujada por 0.5h y diluida con agua. Después de enfriarla a temperatura ambiente, el sólido separado fue filtrado y secado para dar 2-metoxi-4(metilamino)-5-nitrofenol como un sólido rojo. MS: MH+ 198.

Paso 4. Síntesis de {4-[2-metoxi-4-(metilamino)-5-nitrofenoxi](2-piridil)}-N-metilcarboxamida.

A una solución agitada de 2-metoxi-4(metilamino)-5-nitrofenol (1 eq) en N,N-dimetilacetamida se le agregó potasio-t-butóxido (1.2 eq) y se continuó agitando a temperatura ambiente hasta que se solidificó. A esto se agregó (3-clorofenil)-N-metilcarboxamida (1 eq) y carbonato de potasio anhídro (1 eq) y la mezcla resultante fue calentada a 50° C mientras el sólido se licuaba. Luego fue calentada a 110° C por 12h. Después de enfriar a temperatura ambiente se destiló el solvente y el sólido resultante fue extraido usando etil acetato en un aparato "soxhlet" por 48h. La capa orgánica fue enfriada a 0° C y cuando el producto

cristalizó del etil acetato dió {4-[2-metoxi-4-(metilamino)-5-nitrofenoxi](2-piridil)}-N-metilcarboxamida.Ms: MH+ 332.

Paso 5. Síntesis de 4-{2-[(4-clorofenil)amino]-6-metoxi-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico.

A tert-butil-4-[3-amino-6-metoxi-4-(metilamino)fenoxi]piridin-2-carboxilato (1 eq) en metanol se le agregó 4-clorobencenisotiocianato (1 eq) y se agitó a temperatura ambiente por 6h. La formación de la correspondiente tioúrea fue seguida por LS/MS. A esto se agregó iodometano (1 eq) y fue calentado a 60° C por 2 horas. La formación de tert-butil-4-(2-{[4-clorofenil]amino}-1-metilbencimidazol-5-iloxi)piridin-2-carboxilato fue seguida por LC/MS. A esto en cloruro de metileno fue agregado ácido trifluoroacético y agitado a temperatura ambiente durante la noche. El producto resultante 4-{2-[(4-clorofenil)amino]-6-metoxi-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico fue purificado por cromatogRafía preparativa. MS; MH+ = 424.

Paso 6. Síntesis de [4-(2-{[4-clorofenil]amino-6-metoxi-1-metilbencimidazol-5-iloxi}(2-piridin))]-N-(2-pirrolidiniletil)carboxamida.

A 4-{2-[(4-clorofenil)amino]-6-metoxi-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico (1 eq) en tetrahidrofurano fue agregado 2-pirrolidiniletilamina (2 eq), HBTU (2 eq) y N,N-diisopropiletilamina (4 eq) y agitado a temperatura ambiente por 16h. La mezcla fue luego concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y la cromatogRafía preparativa dió el producto [4-(2-{[4-clorofenil]amino-6-metoxi-1-metilbencimidazol-5-iloxi}(2-piridin))]-N-(2-pirrolidiniletil)carboxamida. MS: MH+ = 522.

Ejemplo 700

Paso 1. Síntesis de 4-{2-[(4-bromo-3-metilfenil)amino]-6-metoxi-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico.

A tert-butil-4-[3-amino-6-metoxi-4-(metilamino)fenoxi]piridin-2-carboxilato (1 eq) en metanol se le agregó 4-bromo-3-metilbencenisotiocianato (1 eq) y agitado a temperatura ambiente por 16h. La formación de la correspondiente tioúrea fue seguida por LC/MS. A esto fue agregado iodometano (1 eq) y calentado a 60° C por 2h. La formación de ter-butil-4-(2-{[4-bromo-3-metilfenil]amino}-1-metilbencimidazol-5-iloxi)piridin-2-carboxilato fue seguida por LC/MS. A esto en cloruro de metileno se agregó ácido trifluoroacético y fue agitado a temperatura ambiente durannte la noche. El resultado 4-(2-{[4-bromo-3-metilfenilamino]-6-metoxi-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico fue purificado por cromatogRafía preparativa. MS: MH+ = 482.

Paso 2. Síntesis de [4-(2-{[4-bromo-3-metilfenil]amino-6-metoxi-1-metilbencimidazol-5-iloxi}2-piridin)]-N-2-pirrolidiniletilcarboxamida.

A 4-(2-{[4-bromo-3-metilfenilamino]-6-metoxi-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico (1 eq) en tetrahidrofurano fue agregado 2-pirrolidiniletilamina (2 eq), HBTU (2 eq) y N,N-diisopropiletilamina (4 eq) y agitado a temperatura ambiente por 16h. La mezcla fue luego concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y la cromatogRafía preparativa dió como resultado 4-{2-[(4-bromo-3-metilfenil)amino]-6-metoxi-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico.

Ejemplo 701

Paso 1. Síntesis de 4-{3-[3-(3-isopropilfenil)-tioúreaido]-4-metilamino-fenoxi}piridin-2-ácido carboxílico.

A tert-butil-4-[3-amino-4-(metilamino)fenoxi]piridin-2-carboxilato (1 eq) en metanol fue agregado 3-isopropilbencenisotiocianato (1 eq) y agitado a temperatura ambiente por 16h. La formación de la correspondiente tioúrea fue seguida LC/MS. A esto fue agregado iodometano (1 eq) y calentado a 60° por 2h. La formación de 4-{3-[3-(3-isopropilfenil)-

tioureaido]-4-metilamino-fenoxi}piridin-2-carboxilato fue seguida por LS/MS. A esto en cloruro de metileno fue agregado ácido trifluoroacético y agitado a temperatura ambiente durante la noche. El producto resultante 4-(2-{[4-bromo-3-metilfenil-amino]-1-metilbencimidazol-5-iloxi}piridin-2-ácido carboxílico fue purificado por cromatogRafía preparativa. MS: MH+ = 437.

Paso 2. Síntesis de 4-[2-(3-isopropil-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]piridin-2-ácido carboxílico)-2-pirrolidin-1-il-etil)-amida.

A 4-{3-[3-(3-isopropilfenil)-tioúreaido]-4-metilamino-fenoxi}piridin-2-ácido carboxílico (1 eq) en tetrahidrofurano fue agregado 2-pirrolidiniletilamina (2 eq) EDCI (2 eq), HOAT (1.2 eq) y N,N-diisopropiletilamina (4 eq) y agitado a temperatura ambiente por 16h. La mezcla fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue concentrada y la cromatogRafía preparativa dió 4-[2-(3-isopropil-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]piridin-2-ácido carboxílico)-2-pirrolidin-1-il-etil)-amida. Ms: MH+ = 499.

Ejemplo 702

Paso 1. Síntesis de 3-cloro-4-(2-metil-5-nitrofenil)piridin.

Nitrógeno fue burbujeado a traves de una solución de 2-bromo-1-metil-4-nitrobenceno (1 eq) en dimetoxietano y agua (3:1) por 0.5h. Bis(difenilfosfino)ferrocenpaladio(II)cloruro (0.05 eq) seguido por 3-cloro-4-piridin-ácido borónico hidratado (1 eq) y carbonato de sodio (3 eq) fueron agregados y la mezcla calentada a 90° C por 16h bajo nitrógeno. La mezcla de reacción fue concentrada y dividida entre etil acetato y agua. La capa orgánica fue lavada con salmuera y secada con sulfato de sodio y concentrada. Purificación sobre silica gel dió como resultado 3-cloro-4-(2-metil-5-nitrofenil)piridin. MS: MH+ = 248.

Nota: El mismo procedimiento fue utilizado para la reacción de Susuki entre halopiridinas y los ácidos nitrofenilborónicos.

Los ácidos borónicos fueron sintetizados usando el siguiente procedimiento que no está comercialmente disponible.

Paso 1 . Síntesis de 2-fluoropiridin-ácido borónico.

Un frasco secado a la llama fue cargado con tolueno y tetrahidrofurano (4:1) y luego con 4-bromo-2-fluoropiridin (1 eq) y triisopropilborato (1.2 eq) y el frasco fue enfriado a menos 70°C. Luego n-butil-litio (1.2 eq) fue agregado por gotas en 0.5h y la mezcla fue agitada por 0.5h a -70° C. La mezcla de reacción fue luego traida a -20° C y 2N-ácido hidroclorídrico le fue agregado. La formación de 2-fluoropiridin ácido borónico fue vista por LC/MS mientras se calentaba la mezcla a temperatura ambiente. La mezcla fue dividida entre etil acetato y agua. La capa orgánica fue secada con sulfato de sodio y concentrada para dar como resultado 2-fluoropiridin-ácido borónico. MS: MH+ = 141.

Paso 2. Síntesis de 3-(3-cloro(4-piridin)-4-metilfenilamina.

A la mezcla conteniendo 3-cloro-4-(2-metil-5-nitrofenil)piridina en ácido acético se agregó polvo de Fe (5 eq) y la mezcla resultante fue agitada a temperatura ambiente por 6h. A esto fue agregado carbonato de sodio saturado para traerla a pH neutral y extraída con etil acetato. La capa orgánica fue lavada con salmuera, secada con sulfato de sodio, concentrada y pasada a través de una capa de silica para dar 3-(3-cloro(4-piridin)-4-metilfenilamina.

Paso 3. Síntesis de 3-(3-cloro(4-piridin)-4-metilbencenisotiocianato.

A 3-(3-cloro(4-piridin)-4-metilfenilamina en acetona a 0° C fue agregado carbonato de sodio (2 eq) y tiofosgeno (2 eq). La mezcla fue traida a temperatura ambiente concentrada y dividida entre etil acetato y agua. La capa orgánica fue secada con bicarbonato de sodio y

sulfato de sodio y concentrada para dar 3-(3-cloro(4-piridin)-4-metilbencenisotiocianato. MS: MH+ = 260.

Paso 4. Síntesis de {4-(2-{[3-(3-cloro(4-piridil))-4-metilfenil]amino}-1-metilbencimidazol-5-iloxi)(2-piridil)}-N-metilcarboxamida.

A 3-(3-cloro(4-piridin)-4-metilbencenisotiocianato (1 eq) en metanol se agregó {4-[3-amino-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida (1 eq) y la mezcla resultante fue agitada a temperatura ambiente por 16h. El LC/MS mostró la formación de la correspondiente tioúrea. A esto en metanol le fue agregado cloruro ferrico anhidro (1.5 eq) y agitado por 3h. La mezcla de reacción fue luego concentrada a la mitad de su volumen y traida a pH neutral con 1N hidroxido de sodio. Luego fue extraida con etil acetato y la capa orgánica fue lavada con salmuera y secada con sulfato de sodio. El crudo fue luego tratado con metanol caliente para dar {4-(2-{[3-(3-cloro(4-piridil))-4-metilfenil]amino}-1-metilbencimidazol-5-iloxi)(2-piridil)}-N-metilcarboxamida. MS: MH+ = 498.

Ejemplo 703

Paso 1. Síntesis de {4-(2-metoxi-4-(metilamino)-5-nitrofenoxi)(2-piridil)}-N-metilcarboxamida.

A una solución concentrada de ácido nítrico (22 eq) fue agregado 2h-benzo[d]1,3-dioxolano (1 eq) a 0-10° C por 0.5h y agitado por otras 0.5h. A esta mezcla de reacción le fue agregado ácido sulfurico (0.06 eq) a gotas a 0-10° C por 0.5h y agitado a 20° C a 0.5h. Luego fue vertida sobre hielo triturado y el sólido separado fue filtrado, lavado con agua y secado para dar 5,6-dinitro-2h-benzol[d]1,3-dioxolano. MS: MH+ 212.

Paso 2. Síntesis de metil(6-nitro(2h-benzo[3,4.d]1,3,-dioxalano-5-il)amina.

A una solución agitada de metil amina en éter y etanol (1.5:1) se agregó 5,6-dinitro-2h-benzol[d]1,3-dioxolano y agitado a temperatura ambiente por 24h. El solvente fue evaporado

bajo vacio y el sólido fue lavado con agua y secado para dar el producto metil-(6-nitro(2h-benzo[3,4.d]1,3,-dioxalano-5-il)amina. MS: MH+ 196.

Paso 3. Síntesis de 2-metoxi-4-(metilamino)-5-nitrofenol.

A una solución agitada de metanol fue agregado sodio metálico (4.8 eq) lentamente a temperatura ambiente seguido por metil-(6-nitro(2h-benzo[3,4.d]1,3,-dioxalano-5-il)amina (1 eq) y agitado por 2h. La mezcla fue luego reflujada por 0.5h y diluida con agua. Después de enfriarla a temperatura ambiente el sólido separado fue filtrado y secado para dar 2-metoxi-4-(metilamino)-5-nitrofenol como un sólido rojo. MS: MH+ 198.

Paso 4. Síntesis de {4-[2-metoxi-4-(metilamino)-5-nitrofenoxi](2-piridil)}-N-metilcarboxamida.

A una solución de 2-metoxi-4-(metilamino)-5-nitrofenol (1 eq) en N,N-dimetilacetamida fue agregado t-butóxido de potasio (1.2 eq) y continuamente agitado a temperatura ambiente hasta solidificación. A esto fue agregado (3-clorofenil)-N-metilcarboxamida (1 eq) y carbonato de potasio anhidro (1 eq) y la mezcla resultante fue calentada a 50° C mientas el sólido se licuaba. Luego fue calentada a 110° C por 12h. Luego de enfriar a temperatura ambiente, fue destilada y el sólido resultante extraído usando etil acetato en un aparato "soxhlet" por 24h. La capa orgánica fue enfriada a 0° C cuando el producto cristalizado del etil acetato dió como resultado {4-[2-metoxi-4-(metilamino)-5-nitrofenoxi](2-piridil)}-N-metilcarboxamida. MS: MH+ 332.

Paso 5. Síntesis de {4-[3-amino-6-metoxi-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida.

Una solución {4-[2-metoxi-4-(metilamino)-5-nitrofenoxi](2-piridil)}-N-metil-carboxamida, en metanol fue hidrogenada con 10% Pd/C. El catalizador fue filtrado y el

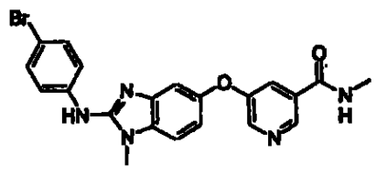
solvente fue concentrado para dar como resultado 4-[3-amino-6-metoxi-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida.

Paso 6. Síntesis de (4-{2-[(4-bromo-3-metilfenil)amino]-6-metoxi-1-metil-bencimidazol-5-iloxi}-(2-piridil))-N-metiolcarboxamida.

A una solución de 4-[3-amino-6-metoxi-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboxamida.(1 2q) en metanol se agregó 4-bromo-3-metilbencenisotiocianato (1 eq) y agitado a 60° C por 2h. La formación de tioúrea fue seguida por LC/MS. A esto se agregó iodometano (1 eq) y se calentó a 60° C por 3h. La mezcla fue concentrada y purificada en cromatogRafía preparativa para dar (4-{2-[(4-bromo-3-metilfenil)amino]-6-metoxi-1-metilbencimidazol-5-iloxi}-(2-piridil))-N-metilcarboxamida. MS:MH+496.

Ejemplo 704

Síntesis de (5-{-2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}-(3 piridil)-N-metilcarboxamida



Paso 1 Sintesis de metil-5-(4-nitrofenoxi)piridin-3-carboxilato

La mezcla conteniendo metil-5-(4-hidroxipiridin-3-carboxilato (1 eq), potasio-bis(trimetilsilil)amida (1.2 eq) fue agitada en N;N-dimetilformamida por 2 h a temperatura ambiente. A esta mezcla se agregó 1-fluoro-4-nitrobenceno (1.1eq) y carbonato de potasio (1.2 eq) y agitada a 80 ° C por 16 h. La mezcla de reacción fue luego concentrada y dividida entre etil acetato y agua. La capa orgánica fue separada y lavada con salmuera, secada, filtrada y concentrada al vacío para dar un solido café. La purificación con sílica dió metil-5-(4-nitrofenoxi)piridin-3-carboxilato. MS:MH+= 274.

Paso 2 Síntesis de metil-5-[4-aminofenoxi]piridin-3-carboxilato.

La mezcla conteniendo metil-5-(4-nitrofenoxi)piridine-3-carboxilato en metanol con una cantidad catalítica de 10% Pd/C fue hidrogena para dar de metil-5-[4-aminofenoxi]piridin-3-carboxilato. MS:MH+= 244.

Paso 3 Síntesis de metil-5-[4-(2,2,2,-trifuoroacetamino)fenoxi]piridin-3-carboxilato

Una solución de metil-5-[4-aminofenoxi]piridin-3-carboxilato (1 eq) en cloruro de metileno fue tratada con ácido trifluoroacético (1 eq) y agitada por 10 minutos a 0° C. La mezcla fue apagada con solución saturada de bicarbonato de sodio. La capa orgánica fue separada y lavada con agua y salmuera, secada y evaporada para dar 5-[4-(2,2,2,-trifuoro-acetamino)fenoxi]piridin-3-carboxilato. MS:MH+=340.

Paso 4 Síntesis de metil-5-[3-nitro-4-(2,2,2,-trifluoroacetilamino)fenoxi]piridin-3-carboxilato

A una solución de 5-[4-(2,2,2,-trifuoro-acetamino)fenoxi]piridin-3-carboxilato en ácido acético y anhídrido acético (1:1) a 0° C. fue agregado ácido nítrico seguido de ácido sulfúrico. Siguiendo la reacción por LC y una vez completa, se dividió entre etil acetato y agua. La capa orgánica fue lavada con salmuera y secada con sulfato de sodio para dar metil-5-[3-nitro-4-(2,2,2,-trifluoroacetilamino)fenoxi]piridin-3-carboxilato. MS:MH+= 385

Paso 5 Síntesis de metil 4- [4-(metilamino)-3-nitrofenoxi]piridin-3-carboxilato

A la solución de metil-5-[3-nitro-4-(2,2,2,-trifluoroacetilamino)fenoxi]piridin-3-carboxilato (1 Eq) en una mezcla de tolueno, acetonitrilo y solución de hidróxido de sodio (50%) se agregó benciltrimetilamonio cloruro (1 eq) y dimetil sulfato (1.2 eq). La mezcla bifásica fue agitada durante la noche a temperatura ambiente y evaporada. La mezcla fue tomada en etil acetato, lavada con agua y salmuera, secada y evaporada. El crudo fue

purificado por columna cromatográfica para dar metil 4- [4-(metilamino)-3-nitrofenoxi]piridin-3-carboxilato. MS:MH+= 303.

Paso 6. Síntesis de metil-5-[3-amino-4-(metilamino)fenoxi]piridin-3-carboxilato

La mezcla conteniendo metil 4- [4-(metilamino)-3-nitrofenoxi]piridin-3-carboxilato fue hidrogenda con 10%Pd/C para dar metil-5-[3-amino-4-(metilamino)fenoxi]piridin-3-carboxilato. MS:MH+= 273

Paso 7. Síntesis de metil-5-{2[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}piridin carboxilato

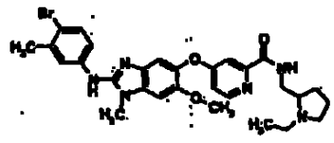
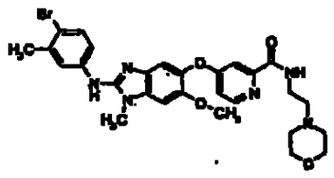
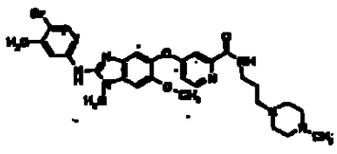
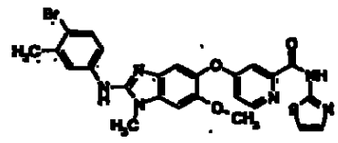
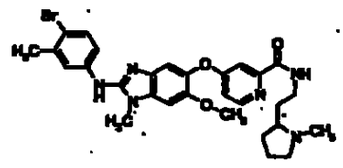
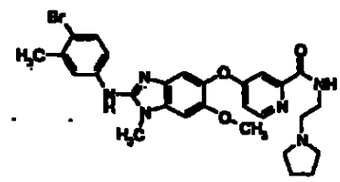
Una solución de metil-5-[3-amino-4-(metilamino)fenoxi]piridin-3-carboxilato (1 eq) en metanol (8 ml) fue tratada con 4-bromofenilisotiocianato (1eq) y agitada a 60° C-65° C por 2 h. La mezcla de reacción fue enfriada a temperatura ambiente, evaporada, tomada en etil acetato y lavada con agua y salmuera, secada, evaporada bajo presión reducida. La columna de cromatogRafía dió metil-5-{2[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}piridin carboxilato. MS:MH+= 452.

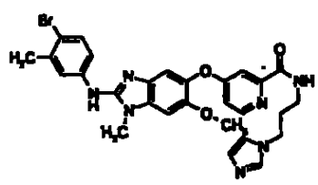
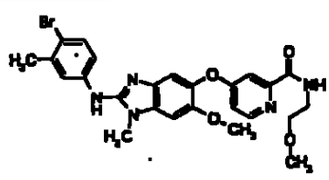
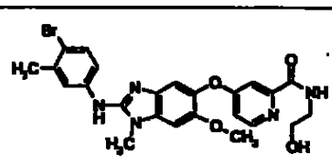
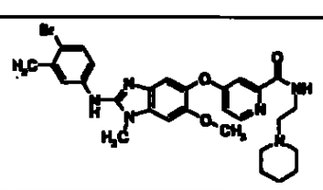
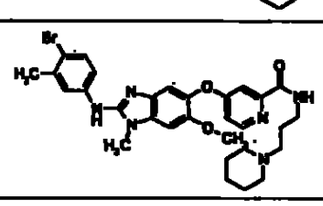
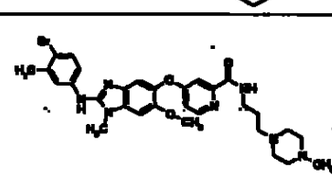
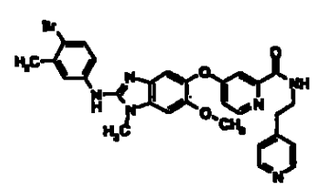
Paso 8. Síntesis de (5-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}-(3-piridil)-N-metilcarboxamida

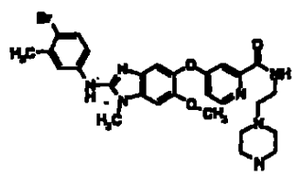
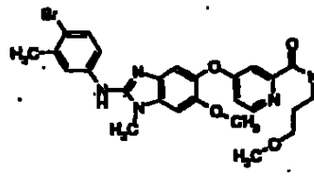
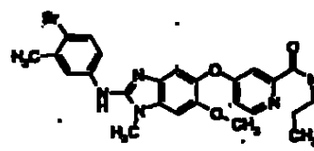
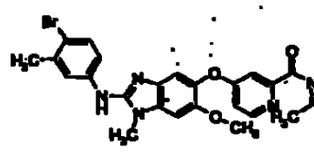
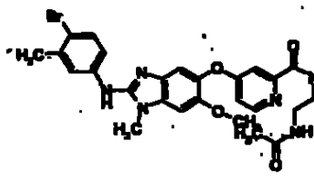
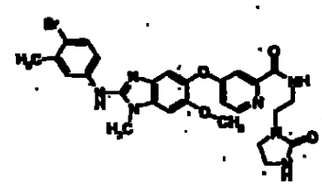
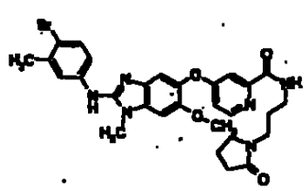
A una solución de metil-5-{2[(4-bromofenil)amino]-1-metil-bencimidazol-5-iloxi}piridin carboxilatose agregó metilamina y la mezcla resultante fue agitada a temperatura ambiente por 16 h. Fue luego concentrada y purificada por cromatogRafía preparativa para dar (5-{2-[(4-bromofenil)amino]-1-metilbencimidazol-5-iloxi}-(3-piridil)-N-metilcarboxamida. MS:MH+=452.

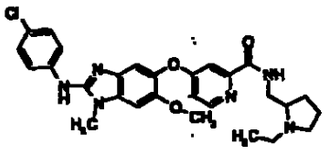
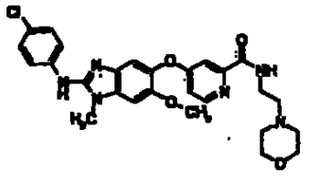
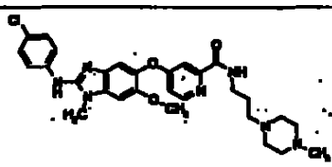
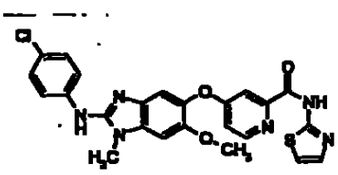
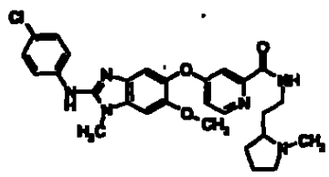
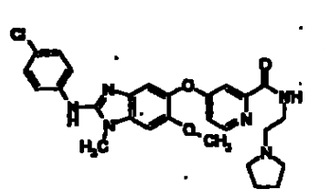
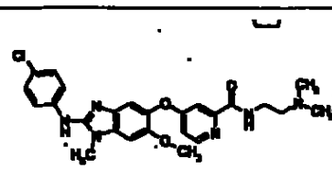
Cada uno de los compuestos 705-746, listados en la Tabla 8, fueron sintetizados como se indica en la columna de la derecha por el método descrito en uno de los ejemplo 699-700.

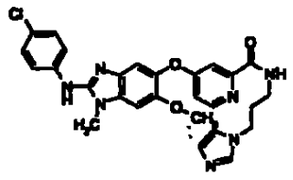
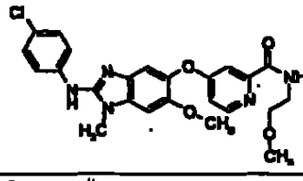
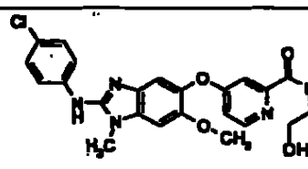
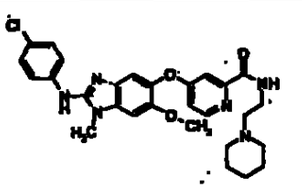
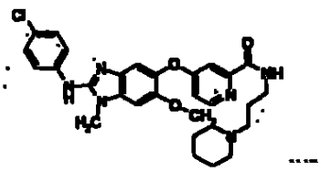
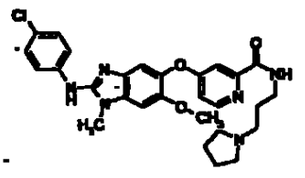
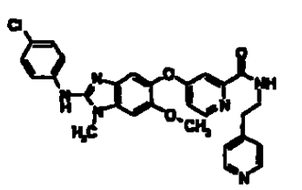
Tabla 8

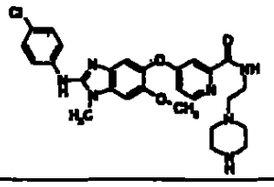
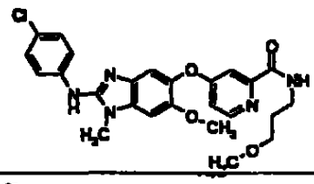
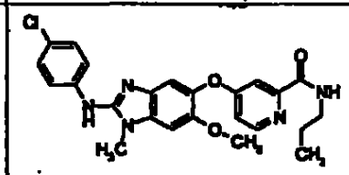
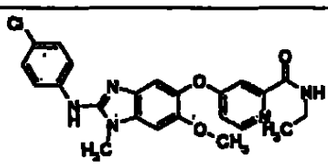
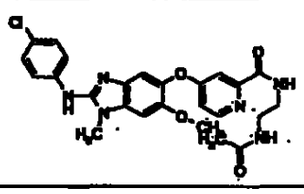
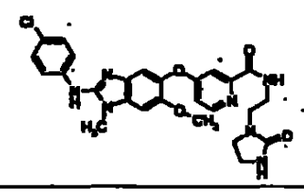
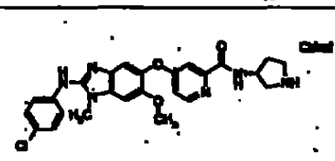
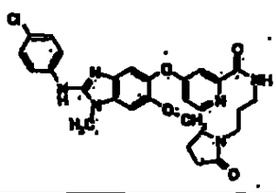
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
705		4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[(1-etil-pirrolidin-2-il)metil]-piridin-2-carboxamida	594.5	700
706		4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-morfolin-4-iletil)piridin-2-carboxamida	596.5	700
707		4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(4-metil-piperazin-1-il)propil]-piridin-2-carboxamida	623.6	700
708		4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-1,3-tiazol-2-ilpiridin-2-carboxamida	566.5	700
709		4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[2-(1-metil-pirrolidin-2-il)etil]piridin-2-carboxamida	594.5	700
710		4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-pirrolidin-1-iletil)piridin-2-carboxamida	580.5	700

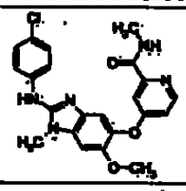
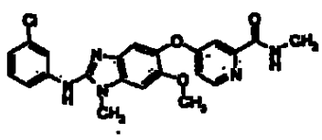
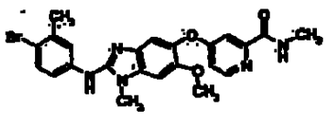
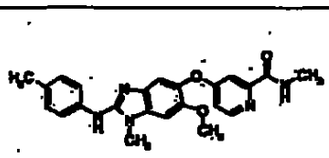
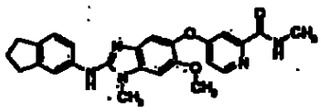
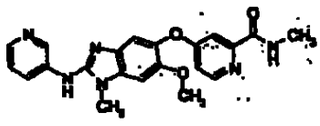
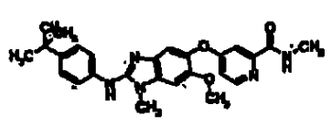
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
711		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(1H-imidazol-1-il)propil]piridin-2-carboxamida	591.5	700
712		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[2-(metiloxi)-etil]piridin-2-carboxamida	541.4	700
713		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-hidroxietil)-piridin-2-carboxamida	527.4	700
714		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-piperidin-1-iletil)-piridin-2-carboxamida	594.5	700
715		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(3-piperidin-1-ilpropil)-piridin-2-carboxamida	608.5	700
716		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(4-metil-piperazin-1-il)propil] piridin-2-carboxamida	623.6	700
717		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-piridin-4-il-etil)-piridin-2-carboxamida	588.5	700

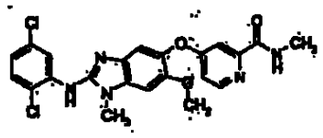
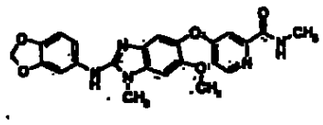
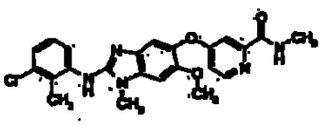
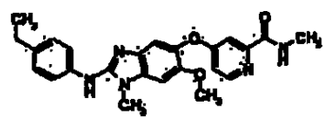
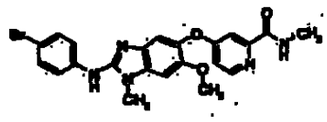
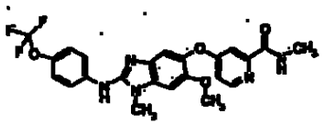
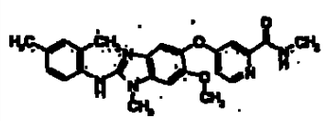
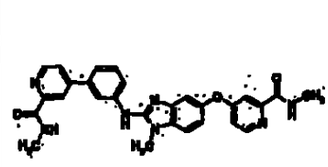
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
718		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-piperazin-1-il-etil)piridin-2-carboxamida	595.5	700
719		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(metiloxi)propil]piridin-2-carboxamida	555.4	700
720		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-propil-piridin-2-carboxamida	525.4	700
721		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-etil-piridin-2-carboxamida	511-4	700
722		N-[2-(acetilamino)etil]-4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1-H—bencimidazol-5-il]oxi}piridin-2-carboxamida	568.4	700
723		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[2-(2-oxo-imidazolidin-1-il)etil] piridin-2-carboxamida	595.5	700
724		4-{[2-[(4-bromo-3-metil-fenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(2-oxo-pirrolidin-1-il)propil]-piridin-2-carboxamida	608.5	700

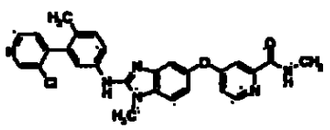
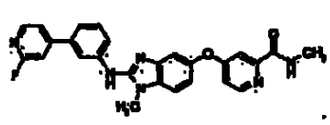
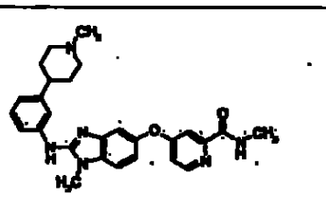
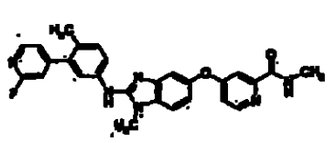
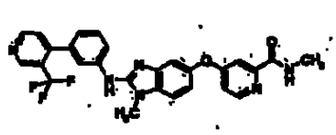
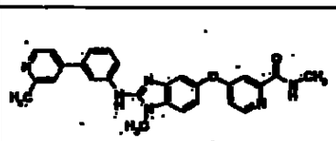
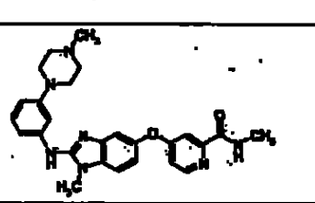
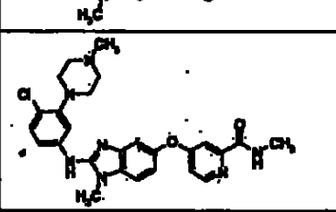
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
725		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[(1-etilpirrolidin-2-il)metil]piridin-2-carboxamida	536.0	69
726		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-morfolin-4-il-etil)piridin-2-carboxamida	538-0	699
727		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	565.1	699
728		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-1,3-tiazol-2-il-piridin-2-carboxamida	508-0	699
729		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[2-(1-metil-pirrolidin-2-il-etil]-piridin-2-carboxamida	536-0	699
730		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-pirrolidin-1-il-etil)-piridin-2-carboxamida	522.0	699
731		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[2-dimetilamino)-etil]-piridin-2-carboxamida	608.5	700

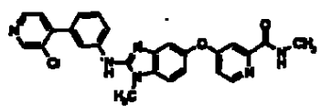
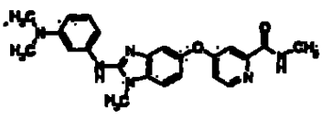
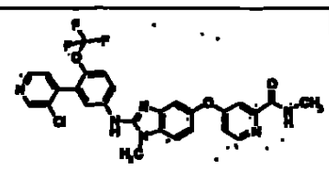
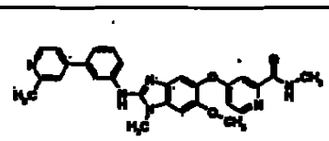
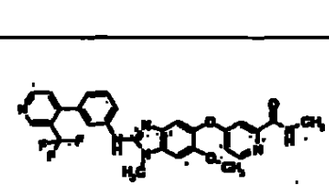
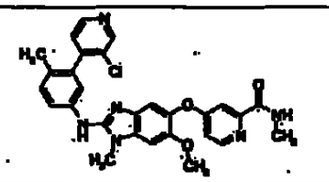
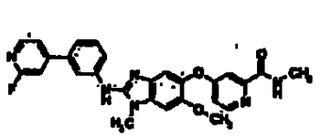
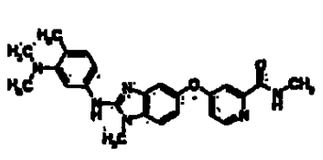
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
732		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N [3-(1H-imidazol-1-il)propil]piridin-2-carboxamida	533.0	699
733		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[2-(metiloxi)etil]piridin-2-carboxamida	482.9	699
734		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-hidroxietil)-piridin-2-carboxamida	468.9	699
735		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-piperidin-1-il-etil)piridin-2-carboxamida	536-0	699
736		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(3-piperidin-1-il-propil)-piridin-2-carboxamida	550.1	699
737		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(3-pirrolidin-1-il-propil)-piridin-2-carboxamida	536.0	699
738		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-piridin-4-iletil)-piridin-2-carboxamida	530	699

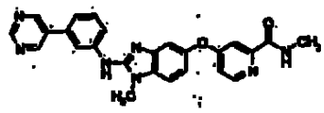
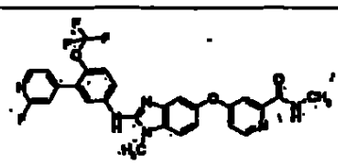
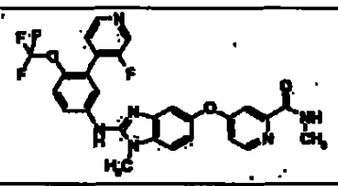
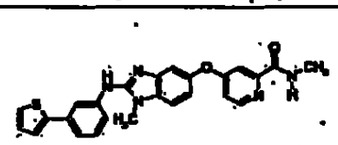
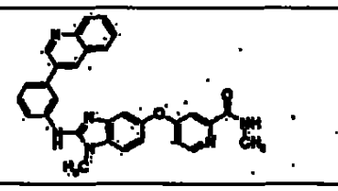
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
739		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-(2-piperazin-iletil)-piridin-2-carboxamida	537.0	699
740		4-{[2-[(4-clorofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(metiloxi)-propil]piridin-2-carboxamida	497.0	699
741		4-{[2-[(4-clorofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-propilpiridin-2-carboxamida	466.9	699
742		4-{[2-[(4-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-etilpiridin-2-carboxamida	452.9	699
743		N-[2-(acetilamino)etil]-4-{[2-[(4-clorofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-piridin-2-carboximida	537.0	699
744		4-{[2-[(4-clorofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[2-(2-oxo-imidazolidin-1-il)etil]-piridin-2-carboxamida	537.0	699
745		4-{[2-[(4-clorofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[(3R)-pirrolidin-3-il]piridin-2-carboxamida	494.0	699
746		4-{[2-[(4-clorofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-[3-(2-oxopirrolidin-1-il)propil]piridin-2-carboxamida	550.0	699

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
747		4-{[2-[(4-clorofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	438.9	703
748		4-{[2-[(3-clorofenil) amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-etilpiridin-2-carboxamida	438.9	703
749		4-{[2-[(4-bromo-3-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	497.4	703
750		N-metil-4-({1-metil-6-(metiloxi)-2-[(4-metil-fenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboximida	418.5	703
751		4-{[2-(2,3-dihidro-1H-inden-5-ilamino)-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	444.5	703
752		N-metil-4-{[1-metil-6-(metiloxi)-2-(piridin-3-il-amino)-1H-bencimidazol-5-il]oxi}-piridin-2-carboximida	405.4	703
753		4-{[2-{[4-(1,1-dimetiletil)-fenil]amino}-1-metil-6-(metiloxi) 1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	460.5	703

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
754		4-{[2-[(2,5-diclorofenil)-amino]-1-metil-6-(metil-oxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	473.3	703
755		4-{[2-(1,3-benzodioxol-5-ilamimo)-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-etilpiridin-2-carboxamida	448.4	703
756		4-{[2-[(3-cloro-2-metil-fenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	452.9	703
757		4-{[2-[(4-etilfenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	432.5	703
758		4-{[2-[(4-bromofenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	483.3	703
759		N-metil-4-{[1-metil-6-(metiloxi)-2-({4-[(trifluorometil)oxi]fenil}amino)-1H-bencimidazol-5-il]oxi}-piridin-2-carboximida	488.4	703
760		4-{[2-[(2,4-dimetilfenil)amino]-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	432.5	703
761		N-metil-4-(3-{[1-metil-5-({2-[(metilamino)carbonil]-piridin-4-il}oxi)-1H-bencimidazol-2-il]amino}-fenil)piridin-2-carboximida	508.6	703

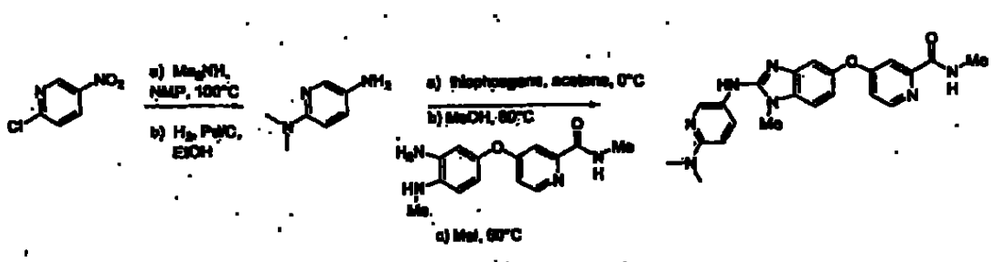
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
762		4-[(2{[3-(3-cloropiridin-4-il)-4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	500.0	702
763		4-[(2{[3-(2-fluoropiridin-4-il)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	469.5	702
764		N-metil-4-[(1-metil-2-{[3-(1-metilpiperidin-4-il)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	471.6	702
765		4-[(2{[3-(2-fluoropiridin-4-il)-4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	483.5	702
766		N-metil-4-[(1-metil-2-({3-[3-(trifluorometil)piridin-4-il]fenil}amino)-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	519.5	702
767		N-metil-4-[(1-metil-2-{[3-(2-metilpiperidin-4-il)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	465.5	702
768		N-metil-4-[(1-metil-2-{[3-(4-metilpiperazin-4-il)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	472.6	702
769		4-[(2{[4-cloro-3-(4-metil-piperazin-1-il-)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	507.0	702

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
770		4-[(2-{[3-(3-cloropiridin-4-il)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	485.9	702
771		4-[(2-{[3-(dimetilamino)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	417.5	702
772		4-{[2-({3-(3-cloropiridin-4-il)-4[(trifluorometil)oxi]fenil}-amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	569.9	702
773		N-metil-4-[(1-metil-6-(metiloxi)-2-{[3-(2-metil-piridin-4-il)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	495.6	702
774		N-metil-4-{[1-metil-6-(metiloxi)-2-({3-[3-(trifluorometil)piridin-4-il]fenil}amino)-1H-bencimidazol-5-il]oxi}-piridin-2-carboxamida	549.5	702
775		4-{[2-{[3-(3-cloropiridin-4-il)-4-metilfenil]amino}-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	530.0	702
776		4-{[2-{[3-(2-fluoropiridin-4-il)fenil]amino}-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	499.5	702
777		4-[(2-{[3-(dimetilamino)-4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida Pagina 165-Borrar	431.5	1

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
778		N-metil-4-({1-metil-2-[(3-pirimidin-5-ilfenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	452.5	702
779		4-{[2-({3-(2-fluoropiridin-4-il)4[(trifluorometil)oxi]fenil}-amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	553.5	702
780		4-{[2-({3-(3-fluoropiridin-4-il)4[(trifluorometil)oxi]fenil}-amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	553.5	702
781		N-metil-4-({1-metil-2-[(3-tien-2-ilfenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	456.5	702
782		N-metil-4-({1-metil-2-[(3-quinolin-3-ilfenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	501.6	702

Ejemplo 783

Síntesis de [4-(2-([6-(dimetilamino)(3piridil)]amino}-1-metilbencimidazol-5-il)oxi}(2-piridil)}-N-metilcarboxamida.

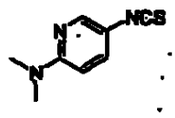


Paso 1. Síntesis de 2-(dimetilamino)-5-nitropiridin:

2-cloro-5-nitro piridina(1.0 eq) y dimeltilamina (2M en EtOH, 4.6 eq) en NMP fueron calentados por 2h a 100°C. La solución fue vertida luego lentamente en agua. El filtrado que se formó fue secado para dar 2-(dimeltilamino)-5-nitropiridina.

Paso 2. Síntesis de 2-(dimetilamino)-5-aminopiridina:

Una mezcla de 2-(dimetilamino)-5-nitropiridina (1eq) y 5% de paladio sobre carbón (0.3 eq) en etanol fue agitada en temperatura ambiente y barrido con N2. El recipiente de reacción fue evacuado y purgada con H_2.tres veces. La mezcla fue dejada bajo una atmósfera de H_2 durante la noche. Nitrógeno fue insuflado a través de la reacción y luego esta fue filtrada a través de una almohadilla de celita. La almohadilla de celita fue lavada con exceso de etanol y antes de que el solvente fuera removido, por evaporación bajo presión, reducida para dar 2-(dimetilamino)-5-aminopiridina.



Paso 3. Síntesis de 2-(dimetilamino)-5-isotiocianato piridina:

2-(dimetilamino)-5-aminopiridina (1.0 eq) fue tomado en acetona y enfriado a 0°C. Tío fosgeno (1.6 eq) fue añadido a cuenta gotas y la reacción fue agitada por 30 minutos a 0°C antes que el exceso de tiofosgeno y acetona fueran removidos por evaporación bajo presión reducida.

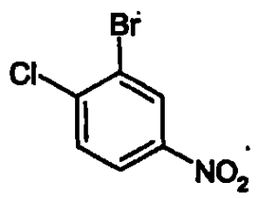
Paso 4. Síntesis de [4-(2-{[6-(dimetilamino)(3-piridil)]amino}-1-metil-bencimidazol-5-iloxy)(2-piridil)}-N-metilcarboxamida.

Una solución de {4-[3-amino-4-(metilamino)fenoxi](2-piridil)}-N-metilcarboximida (1.1 eq) en metanol fue tratada con 2-(dimetilamino)-5-isotiocianatopiridina (1.0 eq) y agitado a 60°C por 2h. Ioduro de metilo (1 eq) fue añadido y agitado durante la noche a 60°C. La

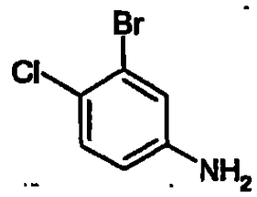
reacción fue enfriada a temperatura ambiente, evaporada y purificada por HPLC de fase reversa. MS: MH+=418.3.

Ejemplo 784

Paso 1



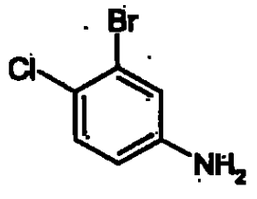
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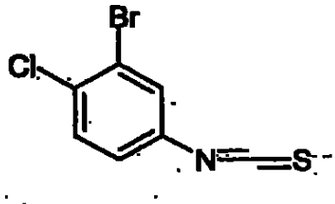
2

Una solución de 1 (1 eq) y 10% de paladio sobre carbón (0.1 eq) en etil acetato fue agitada a temperatura ambiente y fue insuflada con nitrógeno. Hidrógeno fue insuflado a través de la reacción por 2-3h o hasta que ésta fue completada y determinada por HPLC. Nitrógeno fue insuflado a través de la reacción por 15 minutos antes de que esta fuera filtrada a través de una almohadilla de celita. La almohadilla de celita fue lavada con exceso de etil acetato y cloruro de metileno antes de que la solución orgánica combinada fuera removida por evaporación bajo presión reducida para refinar el producto como un sólido 2. MS:MH+ =207.

Paso2.



2

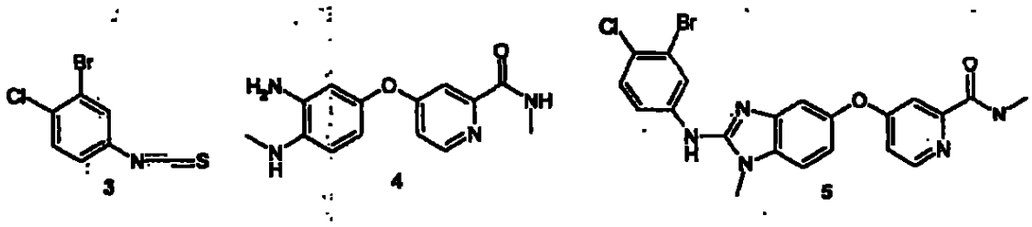


3

Una solución de 2(1 eq) carbonato de sodio (1.5 eq) en acetona fue agitada bajo nitrógeno en un baño de hielo. Tiofosgeno(1.5 eq) fue añadido a cuenta gotas durante 30

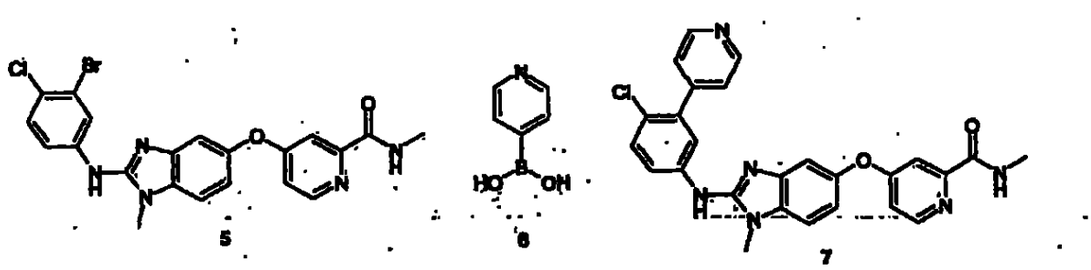
minutos. La reacción fue agitada por otros treinta minutos en el baño de hielo antes de que fuera removida y se le permitiera bajar a temperatura ambiente. La reacción fue agitada a temperatura ambiente por 1.5h antes de que la solución de reacción fuera concentrada bajo vacío. Tolueno fue añadido al producto crudo y removido bajo vacío para formar un azeotropo con cualquier tíofosgeno residual y dejar el producto 3. MS:MH+ =249

Paso3.



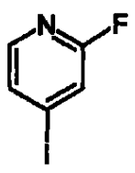
Una solución de 3(1.0 eq) y 4 (1.0 eq) en metanol fue agitada a temperatura ambiente por toda la noche. Cloruro férrico (1.2 eq) fue añadido y la mezcla de reacción resultante estuvo agitada toda la noche a temperatura ambiente. La mezcla de reacción fue concentrada bajo vacío . El producto crudo fue dividido con EtOAc y agua y filtrado. Las capas fueron separadas y la fase acuosa fue neutralizada (pH=7) con solución saturada de carbonato de sodio. La fase acuosa resultante fue extractada con EtOAc. Las capas orgánicas combinadas fueron lavadas con salmuera, secadas con sulfato de sodio y concentradas para dar el producto deseado 5. MS:MH+ = 487.

Paso4.

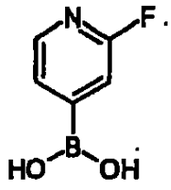


Una solución de 5(1 eq), 6(1 eq) y carbonato de sodio (1.2 eq) DME/H_2O(3:2.1) fue desgasificada por burbujeo de argón a través de la solución por 10 minutos. Pd(II)(dppf)C12-MeC12 (0.1 eq) fue añadido a la solución de reacción y la reacción fue sellada. La reacción fue calentada a 100°C toda la noche, luego, fue enfriada a temperatura ambiente con la adición de etil acetato y agua. La capa orgánica fue separada de la capa acuosa, La capa acuosa fue lavada una vez más con etil acetato. Las capas orgánicas fueron combinadas, secadas con sulfato de sodio y concentradas bajo vacío para rendir el producto deseado 7. MS:MH+ = 469.

Paso5.



8

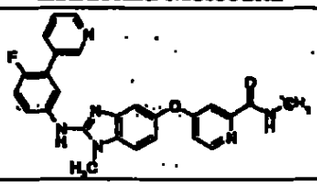
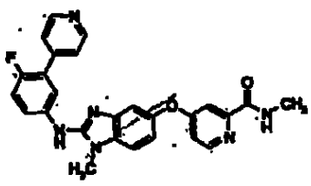
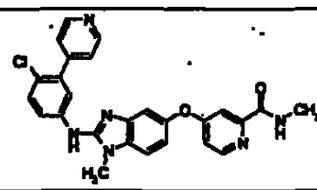
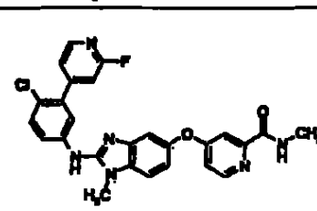
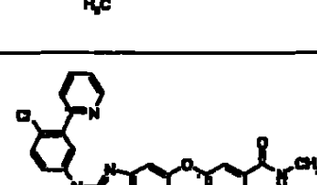
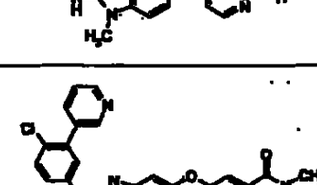


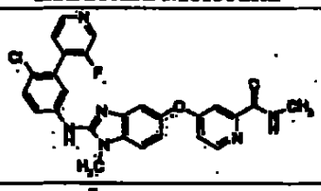
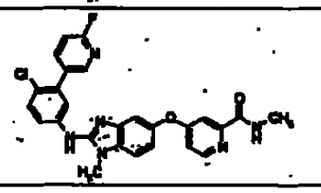
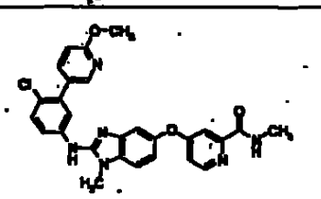
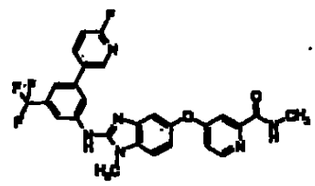
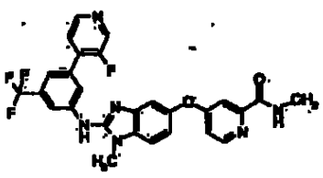
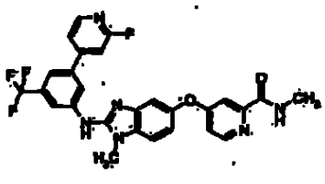
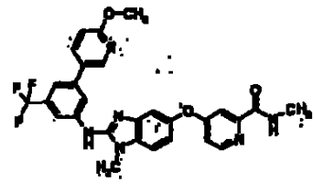
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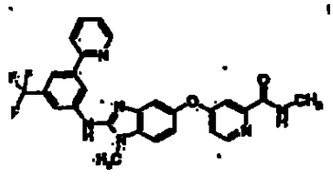
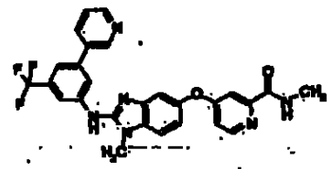
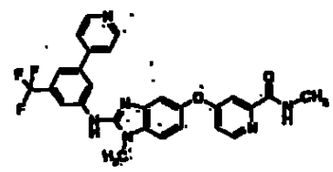
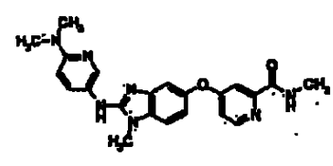
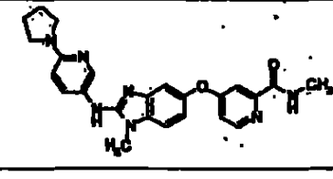
Un frasco de reacción fue secado a la llama y enfriado bajo nitrógeno. Una solución de 8 (1.0 eq) enTHF fue añadido al reactor seguido por borato de tri-isopropil (1.2 eq). La solución de reacción fue colocada en un baño de hielo seco/acetona con agitación a aproximadamente -72°C. N-butil-litio (1.5eq, 2.5M solución.en hexano) fue añadido a cuenta gotas durante 40 minutos. La solución de reacción fue agitada por otros 30 minutos en el baño de hielo seco/acetona, luego fue transferida a un baño de NaCl saturado/hielo seco agitando a aproximadamente -25°C y por 20 minutos antes de que fuera añadido el 2N HCl (2 eq). La solución de reacción luego fue removida del baño para agitarla y calentarla a temperatura ambiente. Las capas orgánicas y acuosas fueron separadas. La acuosa fue lavada una vez con etil acetato mientras que la orgánica fue combinada, secada con sulfato de sodio, y concentrada bajo vacío para rendir el producto deseado 9. MS: MH+ = 141.

Cada uno de los compuestos 785-802, listados en la tabla siguiente fue sintetizado como se indica en la columna derecha por el método descrito en uno de los ejemplos 783 o 784.

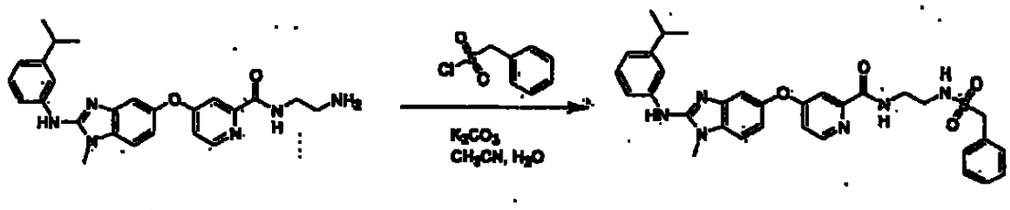
Tabla 10

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
785		4-({2-[(4-fluoro-3-piridin-3-ilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	469.5	784
786		4-({2-[(4-fluoro-3-piridin-4-ilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	469.5	784
787		4-({2-[(4-cloro-3-piridin-4-ilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	485.9	784
788		4-[(2-{[4-cloro-3-(2-fluoropiridin-4-il)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	503.9	784
789		4-({2-[(4-cloro-3-piridin-2-ilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	485.9	784
790		4-({2-[(4-cloro-3-piridin-3-ilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	485.9	784

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
791		4-[(2-{[4-cloro-3-(3-fluoropiridin-4-il)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	503.9	784
792		4-[(2-{[4-cloro-3-(6-fluoropiridin-3-il)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	503.9	784
793		4-[(2-{[4-cloro-3-(6-(metiloxi)-piridin-3-il)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	516.0	784
794		4-[(2-{[4-cloro-3-(6-fluoropiridin-3-il)-5-(trifluorometil)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	537.5	784
795		4-[(2{[3-(3-fluoropiridin-4-il)-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	537.5	784
796		4-[(2{[3-(2-fluoropiridin-4-il)-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	537.5	784
797		N-metil-4-[(1-metil-2-{[3-[6-(metiloxi)piridin-3-il-]-5-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	549.5	784

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
798		N-metil-4-[(1-metil-2-{[3-[3-piridin-2-il-5-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	519.5	784
799		N-metil-4-[(1-metil-2-{[3-[3-piridin-3-il-5-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	519.5	784
800		N-metil-4-[(1-metil-2-{[3-[3-piridin-4-il-5-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	519.5	784
801		4-[(2{[6-(dimetilamino)-piridin-3-il]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	518.5	783
802		N-metil-4-({1-metil-2-[(6-pirrolidin-1-ilpiridin-3-il)-amino]-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	444.5	783

Ejemplo 803

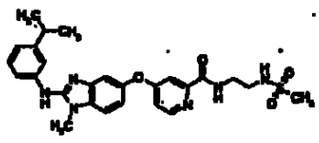
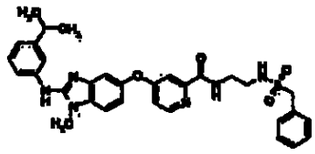
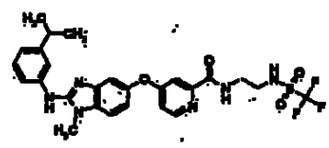


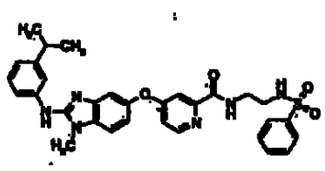
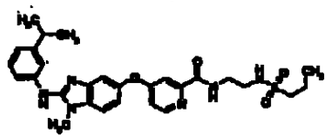
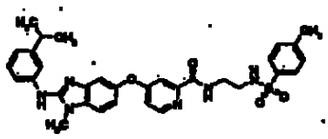
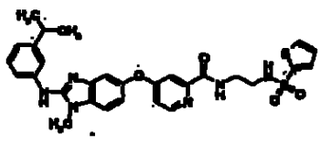
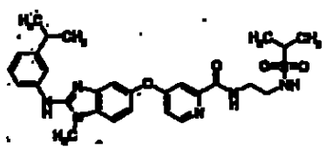
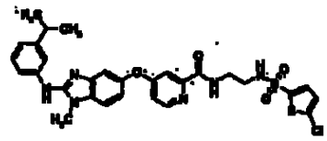
Paso 1. 4-[2-(3-Isopropil-fenilamino)-1-metil-1H-benzoimidazol-5-oxi]-piridin-2-ácido carboxílico (2-fenilmetanosulfonilamino-etil)-amida.

A una mezcla conteniendo 4-[2-(3-isopropil-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico (2-amino-etil)-amida (1 eq) (preparada usando el ejemplo 3 descrito previamente), K_2CO_3 (5 eq), (0.2 M en una mezcla de acetonitrilo y agua 5:1) fueron añadidas α-toluenesulfonilclorhidro (1 eq) vía jeringa. La mezcla heterogénea resultante fue agitada por una hora a temperatura ambiente. La mezcla luego fue diluida con agua y extractada con diclorometano. Los orgánicos fueron lavados con agua y la solución saturada de cloruro de sodio, secada con sulfato de sodio y concentrada *in vacuo* a un aceite viscoso. La purificación por medio de cromatogRafía dió como resultado 4-[2-(3-isopropil-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico (2-fenilmetanosulfonilamino-etil)-amida. MS: MH+ 599.

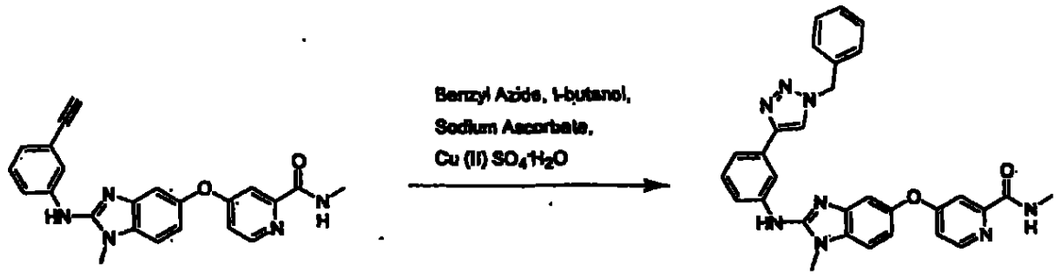
Los compuestos mostrados en la siguiente Tabla (Ejemplos 804- 812) fueron preparados con el procedimiento descrito en el Ejemplo 803.

Tabla 11

Ejemplo	Estructura Molecular	Nombre	MH+
804		4-[(1-metil-2{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-{2-[(metilsulfonil)amino]-etil}piridin-2-carboxamida	523.6
805		4-[(1-metil-2{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-{[(fenilmetil)sulfonil]-amino}etil)piridin-2-carboxamida	599
806		4-[(1-metil-2{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-{[(trifluorometil)sulfonil]-amino}etil)piridin-2-carboxamida	577.6

Ejemplo	Estructura Molecular	Nombre	MH+
807		4-[(1-metil-2{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-{2-[(fenilsulfonil)amino]etil}piridin-2-carboxamida	585.7
808		4-[(1-metil-2{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-{2-[(propilsulfonil)amino]etil}piridin-2-carboxamida	551.7
809		4-[(1-metil-2{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-{[(4-metilfenil)sulfonil]-amino}etil)piridin-2-carboxamida	599.7
810		4-[(1-metil-2{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-{2-[(tien-2-ilsulfonil)amino]etil}piridin-2-carboxamida	591.7
811		N-(2-{[(1-metiletil)-sulfonil]amino}etil)-4-[(1-metil-2-{[3-(1-metiletil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-carboxamida	551.7
812		N-(2-{[(1-metiletil)-sulfonil]amino}etil)-4-[(1-metil-2-{[3-(5-clorotien-2-il)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-carboxamida	626.2

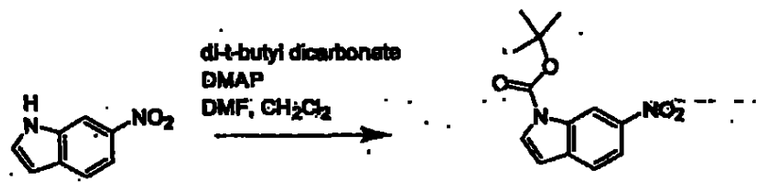
Ejemplo 813



Paso 1. 4-{2-(3-[1-bencil-1H-[1,2,3]tiazol-4-il)-fenil amino]-1-metil-1H-benzoimidazol-5-iloxi}-piridin-2-ácido carboxílico metil amida.

A una mezcla de 4-[2-(3-etil-fenilamino)-1-metil-1H-benzoimidazol-5-il-oxi]-piridin-2-ácido carboxílico metilamida (1 eq) (preparado usando el Ejemplo 2 descrito anteriormente), bencil azida (1 eq) en t-butanol (0.1 M) fue añadida a ascorbate de sodio (0.05 eq), y (II) sulfato de cobre pentahidrato (0.01 eq). La mezcla resultante fue agitada por una hora a temperatura ambiente. La mezcla fue luego disuelta en agua y el sólido recolectado vía succión filtrada. MS: MH+ 531.

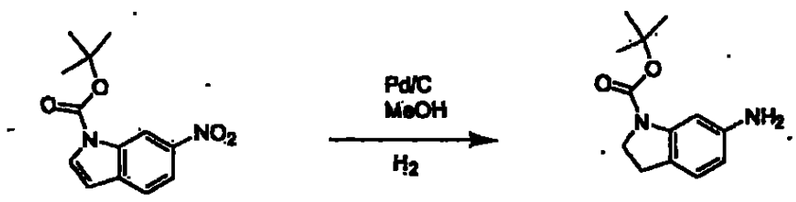
Ejemplo 814



Paso 1. Síntesis de 6-nitro-indol-1-ácido carboxílico t-butil ester.

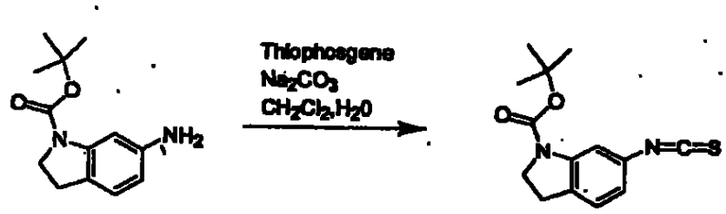
A una solución agitada de 6-nitroindol (1 eq) en diclorometano (0.3 M) y DMF (3.1 M), se le añadió di-t-butil bicarbonato (2 eq) seguido de una adición de 4-(dimetilamino) piridin (1 eq). La solución resultante fue agitada durante la noche a temperatura ambiente. El ciclorometano fue luego removido en una "rotovap" y la solución resultante fue diluida en agua y extractada con etil acetato. Los orgánicos fueron lavados con 10% de solución de

ácido cítrico, una solución de cloruro de sodio saturado, una solución de bicarbonato de sodio saturado, una solución de cloruro de sodio y secada con sulfato de sodio. Etil acetato fue removido a continuación, *in vacuo*. Etil éter fue afiadido posteriormente y un sólido café fue recolectado por filtración de succión para dar 6-nitro-indol-1-ácido carboxílico t-butil ester. MS: MH+ 263.



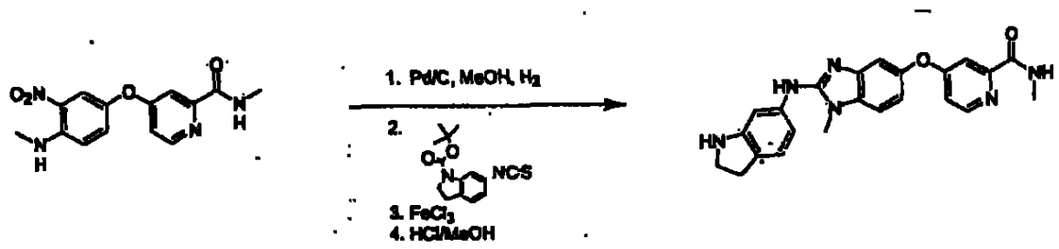
Paso 2. Síntesis de 6-Amino-2,3-dihidro-indol-1-ácido carboxílico t-butil ester.

6-Nitro-indol-1-ácido carboxílico t-butil ester (1 eq) fue disuelto en metanol (0.1 M), a esta solución se le afiadió paladio en carbono (0.1 eq) en metanol bajo nitrógeno. Una atmósfera de hidrógeno fue insertada a continuación y la mezcla resultante fue agitada por 2 horas a 0° C. La mezcla fue disuelta en agua y los orgánicos separados y lavados con agua, una solución saturada de cloruro de sodio y secada con sulfato de sodio, el solvente fue removido *in vacuo* para obtener 6-isotilcianato-2, 3-dihidro-indol-1-ácido carboxílico t-butil ester como aceite naranja.



Paso 3. Síntesis de 6-isotiocianato-2,3-dihidro-indol-1-ácido carboxílico t-butil ester.

Tiofosgeno (1.1.eq) se agregó a una suspensión de 6-amino-2,3-dihidro-indol-1-ácido carboxílico t-butil ester (1 eq), carbonato de sodio (10 eq) y diclorometano con agua 3:2 por volumen a 0° C. la mezcla resultante se agitó por 2 horas a 0° C. La mezcla fue diluida con agua y el producto orgánico, separado y lavado con agua con solución saturada de cloruro de sodio y secado con sulfato de sodio y removido el solvente al vació para dar 6-isotiocianato-2,3-dihidro-indol-1-ácido carboxílico t-butil ester como un aceite color naranja.

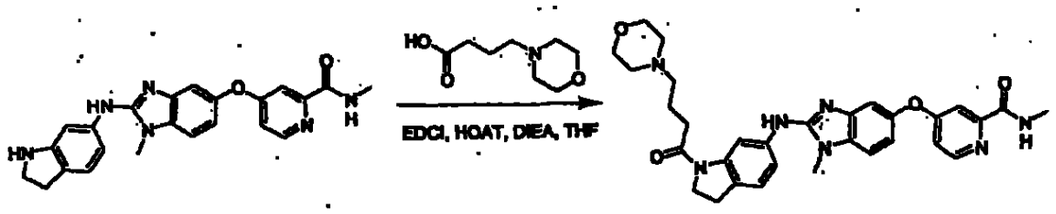


Paso 4. Síntesis de 4-[2-(2,3-dihidro-1H-indol-6-ilamilo)-1-metil-1H-benzoimidazol-5-iloxi] piridin-2-ácido carboxílico metilamida.

A una solución 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-ácido carboxílico metilamida (1 eq) en metanol (0.1 M) fue añadido paladio en carbono (0.1 eq) bajo nitrógeno. La atmósfera fue cambiada por hidrógeno (1 atm) y la suspensión resultante fue agitada por 2 horas a temperatura ambiente. La mezcla fue filtrada por medio de Celite y añadida a 4-isotiocianato-2,3-dihidro-indol-1-ácido carboxílico t-butil ester (1 eq). La solución resultante fue agitada durante la noche. Hierro (III) cloruro (2 eq) en metanol fue añadido y la solución se tornó en un color rojo oscuro. Esta solución fue agitada por 3 horas en temperatura ambiente. Metanol fue luego removido *in vacuo*; el aceite resultante fue disuelto en agua y extraído con diclorometano. Los orgánicos fueron lavados con una solución de bicarbonato de sodio saturado, agua, y una solución de cloruro de sodio saturada y secados con sulfato de sodio. El solvente fue removido *in vacuo*. Al aceite resultante se le añadió tolueno y se

calentó a reflujo, la solución fue enfriada a temperatura ambiente y un sólido fue recolectado luego de 3 días por succión filtrada para obtener 4-[2-(2,3-dihidro-1H-indol-6-ilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico metilamida. MS: MH+ 415.

Ejemplo 815

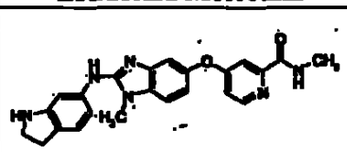


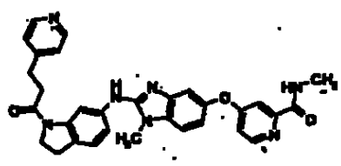
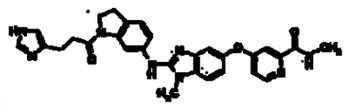
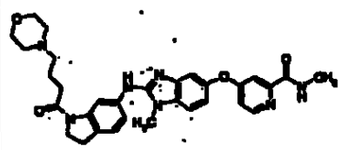
Paso 1. Síntesis de 4-{1-metil-2-[1-(4-morfolin-4-il-butilil)-2,3-dihidro-1H-indol-6-ilamino]-1H-benzoimidazol-5-iloxi}-piridin-2-ácido carboxílico metil-amida.

A una mezcla conteniendo 4-[2-(2,3-dihidro-1H-indol-6-ilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico metilamida (1 eq) (preparada previamente usando Ejemplo 1), EDCI (2 eq), HOAT (1.2 eq), DIEA (4 eq) se le añadió THF. La mezcla fue agitada durante la noche a temperatura ambiente bajo nitrógeno. La mezcla fue luego disuelta en agua, se extrajo con etilacetato. Los orgánicos fueron lavados con agua, luego una solución de cloruro de sodio saturada y secada con sulfato de sodio, filtrada y el solvente removido *in vacuo*. La purificación por cromatogRafía dió como resultado 4-{1-metil-2-[1-(4-morfolin-4-il-butilil)-2,3-dihidro-1H-indol-6-ilamino]-1H-benzoimidazol-5-iloxi}-piridin-2-ácido carboxílico metilamida. MS: MH+ 570.

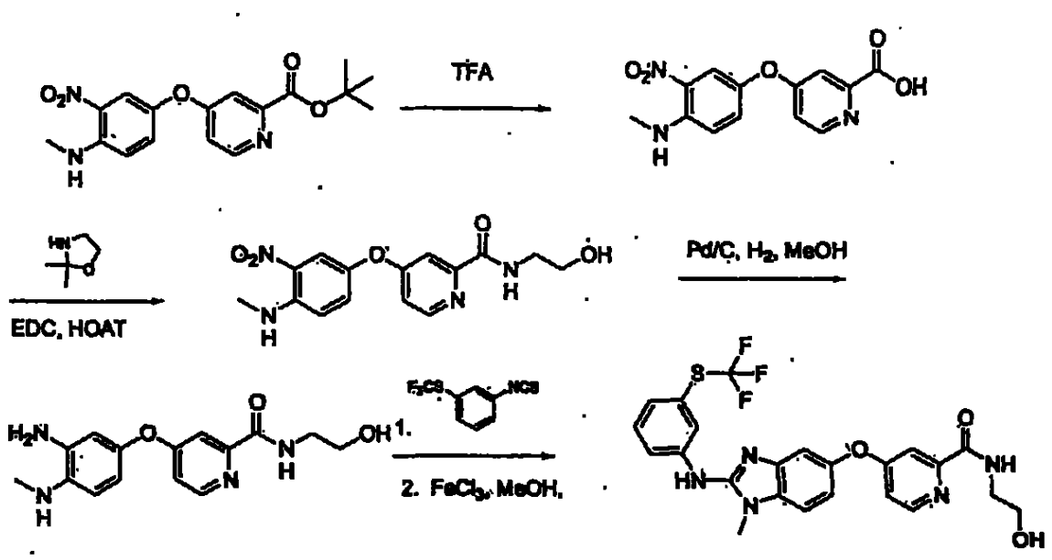
Los compuestos presentados en la siguiente tabla (Ejemplos 816-819) fueron preparados siguiendo el procedimiento descrito en el Ejemplo 815.

Tabla 12

Ejemplo	Estructura Molecular	Nombre	MH+
816		4-{[2-(2,3-dihidro-1H-indol-6-ilamino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	415.5

Ejemplo	Estructura Molecular	Nombre	MH+
817		N-metil-4-[(1-metil-2-{[1-(3-piridin-4-ilpropanoil)-2,3-dihidro-1H-indol-6-il]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	548.6
818		4-{[2-({1-[3-(1H-imidazol-4-il)-propanoil]-2,3-dihidro-1H-indol-6-il}amino)-1-metil-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	537.6
819		N-metil-4-[(1-metil-2-{[1-(4-morfolin-4-ilbutanoil)-2,3-dihidro-1H-indol-6-il]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	570.7

Ejemplo 820



Paso 1. Síntesis de 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-ácido carboxílico.

Una solución agitada de 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-ácido carboxílico tri-t-butil éter en ácido trifluoroacético fue tratada con 2 gotas de agua a temperatura ambiente por 3-4 horas, o cuando la reacción se determinó completa por HPLC. La reacción fue evaporada bajo presión reducida para obtener un aceite naranja rojizo. Una adición de etil éter, "sonication" y filtración produce un sólido rosa claro. LCMS m/z 290.1 (MH+), t_R = 1.71 min.

Paso 2. Síntesis de 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-ácido carboxílico (2-hidroxi-etil)-amida.

A una suspensión de 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-ácido carboxílico (1 eq) en THF seco, EDC-HCl (1.2 eq), HOAT (1.2 eq), y diisopropiletilamina (3 eq) fueron añadidos. La suspensión fue agitada por 10 minutos donde 2,2-dimetil-oxazolidin (1.1 eq) fue añadida y la solución fue agitada durante la noche. La mezcla fue luego disuelta en etil acetato y lavada con agua. La capa acuosa fue lavada con etil acetato, las capas orgánicas combinadas, secadas sobre $MgSO_4$, filtradas, y concentradas. LCMS m/z 333.2 (MH+), t_R = 2.1 min.

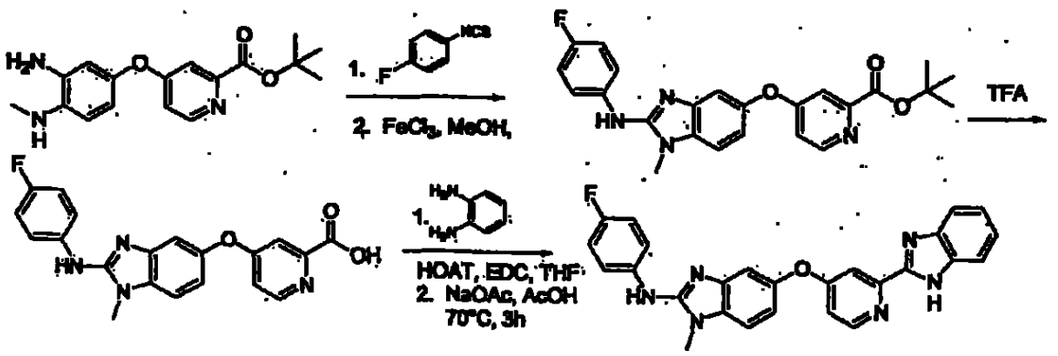
Paso 3. 4-(3-amino-4-metilamino-fenoxi)-piridin-2-ácido carboxílico (2-hidroxi-etil)-amida.

Una solución de 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-ácido carboxílico (2-hidroxi-etil)-amida (1 eq) y 10% de paladio en carbono (0.1 eq) en metanol fue agitada a temperatura ambiente y enjuagada con nitrógeno. El hidrógeno enjuagó la reacción por 1-2 horas o hasta que la reacción fue determinada completa por HPLC. Nitrógeno enjuagó la reacción por 15 minutos antes de que la reacción fuera filtrada por medio de una compresa de Celite. La compresa de Celite fue lavada con exceso de metanol antes de que todo se removiera por medio de la evaporación bajo presión reducida para obtener un sólido amarillo claro. LCMS m/z 303.2 (MH+), t_R = 1.5 min.

Paso 4. 4-[1-metil-2-(3-trifluorometilsulfanil-fenilamino)-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico (2-hidroxi-etil)-amida.

Un frasco fue cargado con 3-(trifluorometiltio)fenilisotiacianato (1 eq), 4-(3-amino-4-metilamino-fenoxi)-piridin-2-ácido carboxílico (2-hidroxi-etil)-amida (1 eq), y MeOH. La reacción fue mantenida a temperatura ambiente durante la noche. Cloruro férrico (1.5 eq), fue añadido y la reacción roja resultante fue agitada durante la noche. La reacción fue separada con EtOAc y agua, y filtrada por medio de Celite. Las capas fueron separadas y la fase acuosa fue neutralizada con una solución de Na_2CO_3 saturada. La fase acuosa resultante fue extraída con EtOAc y la mezcla fue filtrada por medio de Celite. Las fases fueron separadas y nuevamente la fase acuosa fue extraída y filtrada. Las capas orgánicas combinadas fueron lavadas con salmuera, secadas ($MgSO_4$), filtradas y concentradas para dar un sólido café. El residuo crudo fue purificado por HPLC fase-reversible. LCMS m/z 504.1 (MH+), t_R = 3.7 min.

Ejemplo 821



Paso 1. Síntesis de 4[2-(4-fluoro-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico tert-butil ester.

Un frasco de fondo redondo fue cargado con 4-fluorofenilisotiocianato (1 eq), 4-(3-amino-4-metilamino-fenoxi)-piridin-2-ácido carboxílico tert-butil ester (1 eq), y MeOH. La

reacción fue agitada a temperatura ambiente durante la noche. Cloruro férrico (1.5 ep), fue añadido y la mezcla resultante fue agitada durante la noche. La reacción fue separada con EtOAc y agua, y filtrada por medio de Celite. Las capas fueron separadas y la fase acuosa fue neutralizada con una solución de Na_2CO_3 saturada. La fase acuosa resultante fue extraída con EtOAc y la mezcla fue filtrada por medio de Celite. Las fases fueron separadas y la fase acuosa fue de nuevo extraída y filtrada. Las capas orgánicas combinadas fueron lavadas con salmuera, secada sobre $MgSO_4$, filtrada, y concentrada para dar como resultado un sólido café. El residuo crudo fue purificado por trituración en tolueno caliente para obtener el producto deseado. LCMS m/z 435.6 (MH+), t_R = 2.12 min.

Paso 2. Síntesis de 4-[2-(4-fluoro-fenilamino-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico.

Una solución agitada de 4-[2-(4-fluoro-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico tert-butil ester en ácido trifluoroacético fue tratada con dos gotas de agua a temperatura ambiente por 3-4 horas o cuando la reacción se determinará como completa por HPLC. La reacción fue evaporada bajo presión reducida y luego éter fue añadido al residuo, que fue luego "sonicated" por 30 minutos. Filtración y lavado con éter produce el ácido deseado en producto cuantitativo. LCMS m/z 379.4 (MH+), t_R = 1.74 min.

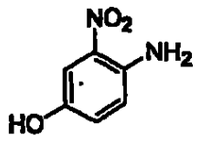
Paso 3. Síntesis de {5.[2-(1H-bencimidazol-2-il)-piridin-4-iloxi]-1-metil-1H-bencimidazol-2-il}-(4-fluoro-fenil)-amina.

A una suspensión de 4-[2-(4-fluoro-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico (1 eq) en THF seco, EDC-HCl (1.2. eq), HOAT (1.2 eq), y diisopropiletilamina (3 eq) fueron añadidas. La suspensión fue agitada por 10 minutos donde fenilenediamina (1.1 eq) fue añadida y la solución fue agitada durante la noche. La mezcla fue luego diluida en etil acetato y lavada con agua. La capa acuosa fue lavada con etil acetato, las

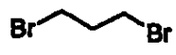
capas orgánicas combinadas, secadas sobre $MgSO_4$, filtradas, y concentradas. Ácido acético fue añadido a un residuo seguido de acetato de sodio (1.1 eq). La mezcla fue calentada por 3 horas a 70° C, donde la solución fue concentrada y el residuo purificado por HLPC fase-reversible para obtener el producto deseado. LCMS m/z 451.5 (MH+), t_R = 1.92 min.

SÍNTESIS DE CADENAS LATERALES

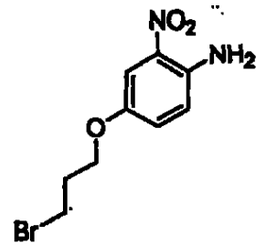
Fenilenediaminas Sustituidos Eter



1



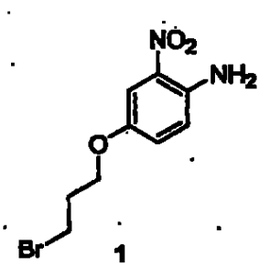
2



3

4-(3-bromopropoxi)-2-nitrofenilamino

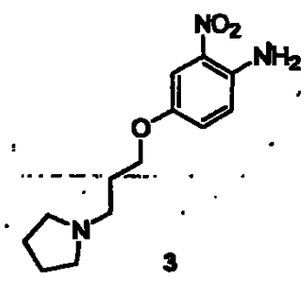
Un frasco es cargado con 4-amino-3-nitrofenol 1 (1 eq), K_2CO_3 (2 eq), y 2-butanona. 1,3-dibromopropano 2 (1.5 eq) es añadido y la mezcla es calentada a 80° C por 18 horas. Luego de enfriarla, la mezcla es filtrada concentrada y se le añadió agua. La solución fue luego extraída con CH_2Cl_2 (X3), la capa orgánica concentrada, y el sólido removido y fue lavada con pentano para producir el producto deseado 3. LCMS m/z 275.1 (MH+), t_R = 2.74 min.



1



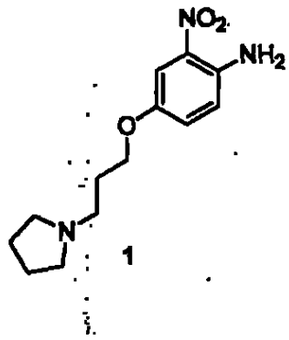
2



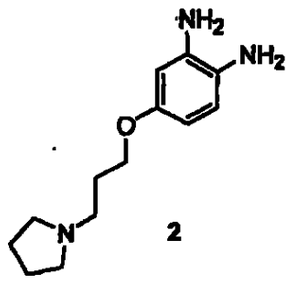
3

2-nitro-4-(3-pirrolidinpropoxi)fenilamina

4-(3-bromopropoxi)-2-nitrofenilamina 1 (1 eq) fue calentada a 70° C con pirrolidin 2 (5 eq) en MeCN con Cs_2CO_3 (2 eq) y Bu_4NI (0.1 eq) por 48 horas. La mezcla de la reacción fue enfriada, filtrada, y concentrada. El residuo fue disuelto en CH_2Cl_2, y lavado con agua. La capa orgánica fue concentrada produciendo el producto deseado 3. LCMS m/z 266.2 (MH+), t_R = 1.51 min.



1

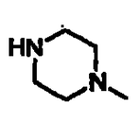


2

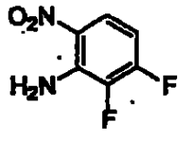
4-(3-pirrolidinpropoxi)benceno-1,2-diamina.

A una solución de 2-nitro-4-(3-pirrolidinpropoxi)fenilamina 1 en EtOH, Pd/C (0.1 eq) es añadido. La vasija de la reacción es purificada repetidamente (X3) con nitrógeno, y luego agitada bajo un atmósfera de hidrógeno por 18 horas. El producto fue filtrado por medio de un tapón de Celite y el tapón lavado con 25 mL de EtOH, para producir 2. LCMS m/z 236.2 (MH+), t_R = 0.94 min.

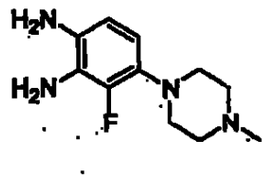
3-fluoro-4-amino fenilenediaminas sustituidas



1



2



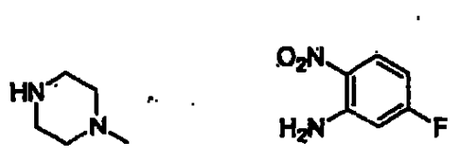
1. Síntesis de 2-fluoro-3-(4-metl-piperazin-1-il)-6-nitro-fenilamina.

Una solución de N-metilpiperzin (1.0 eq), NMP, trietilamina (3.0 eq) y 5,6-difluoro-2-nitroanilina (1.0 eq) fueron calentados a 90° C por una hora. La reacción fue dejada enfriar a temperatura ambiente y luego vertida en agua y dejada reposar por 1 hora. El sólido resultante fue recolectado y secado y utilizado in purificación adicional. MH+ = 255.3.

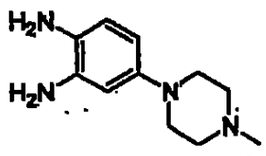
2. Síntesis de 3-fluoro-4-(4-metil-piperazin-1-il)-benceno-1,-diamina.

A una solución de Síntesis de 2-fluoro-3-(4-metil-piperazin-1-il)-6-nitro-fenilamina en EtOH, Pd/C (0.1 eq) fue añadido. La vasija de reacción fue repetidamente purificada (X3) con nitrógeno, y luego agitada bajo una atmósfera de hidrógeno por 18 horas. El producto fue filtrado por medio de un tapón de Celite, el tapón fue lavado con 25 mL de EtOH, para producir la diamina deseada. LCMS 225.3, t_R = 0.45 min.

4-amino fenilenediaminas sustituidas (a)



1 2



Síntesis de 5-(4-metil-piperazin-1-il)-2-nitro-fenilamina.

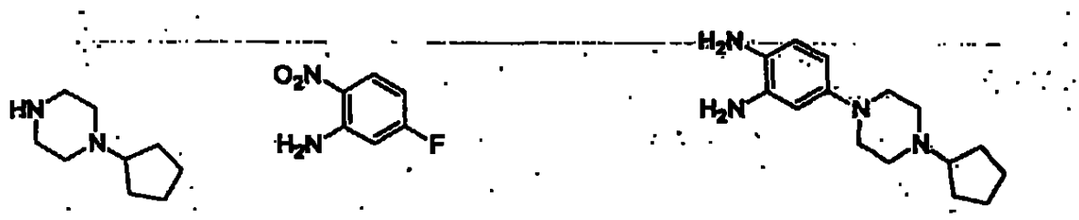
Una solución de N-metilpiperazin (1.0 eq), NMP, trietilamina (3.0 eq) y 5-fluoro-2-nitrofenilamina (1.0 eq) fueron calentadas a 90° C por 1 hora. La reacción fue dejada enfriar a temperatura ambiente y luego vertida en agua y dejada reposar por 12 horas. El sólido resultante fue recolectado y secado y utilizado sin purificación adicional. MH+ = 237.3.

Síntesis de 4-(4-metil-piperazin-1-il)-benceno-1,2-diamina.

A una solución 5-(4-metil-piperazin-1-il)-2-nitro-fenilamina en EtOH, Pd/C (0.1 eq) es añadido. La vasija de reacción fue repetidamente purificada (3X) con nitrógeno, luego agitada

bajo una atmósfera de hidrógeno por 18 horas. El producto fue filtrado por medio de un tapón de Celite, luego el tapón lavado con 25 mL de EtOH, para producir la diamina deseada. LCMS 207.3, t_R = 0.25 min.

4-amino fenilenediaminas sustituidas (b)



1 2

Síntesis de 5-(4-ciclopentil-piperazin-1-il)-2-nitro-fenilamino.

1. Una solución de N-ciclopentilpiperazin (1.0 eq), NMP, trietilamina (3.0 eq) y 5-fluoro-2-nitrofenilamina (1.0 eq) fue calentada a 90° C por una hora. La reacción fue enfriada a temperatura ambiente y luego vertida en agua y dejada reposar por 12 horas. El sólido resultante fue recolectado y secado y utilizado sin purificación adicional. MH+ = 291.4.

2. Síntesis de 4-(4-ciclopentil-piperazin-1-il)-benceno-1,2-diamina.

A una solución 5-(4-ciclopentil-piperazin-1-il)-2-nitro-fenilamino en EtOH, Pd/C (0.1 eq) fue añadido. La vasija de reacción fue purificada repetidamente (X3) con nitrógeno, luego agitada bajo una atmosfera de hidrógeno por 18 horas. El producto fue filtrado por medio de un tapón de Celite, el tapón fue lavado con 25 mL de EtOH, para producir la diamina deseada. MH+ = 261.3.

Ejemplo 822

Paso 1. Síntesis de 4-cloro-piridin-2-ácido carboxílico dimetilamida.

Una solución de 4-cloro-piridin-2-cloruro carbonil (1 eq) en diclorometano fue enfriado a 0° C, donde trietilamina (2 eq) fue añadido seguido de dimetilamina (2 eq, solución 2 M en THF). La solución fue dejada calentar a temperatura ambiente y agitada durante la noche. Luego fue lavada con 1M NaOH. La capa orgánica separada fue secada sobre $MgSO_4$, filtrada y luego concentrada para producir el producto deseado. HPLC, 1.82 min; MH+ = 185.6.

Paso 2. Síntesis de 4-(4-amino-3-nitro-fenoxi)-piridin-2-ácido carboxílico dimetilamida.

Una mezcla conteniendo 4-amino-3-nitrofenil (1 eq) y potasio bis(trimetilsilil)amida (2 eq) fue agitada en dimetilformamida por 2 horas a temperatura ambiente. A la mezcla se le añadió 4-cloro-piridin-2-ácido carboxílico dimetilamida (1 eq) y carbonato de potasio (1.2 eq) y luego agitada a 90° C por 3 días. La mezcla de la reacción fue luego concentrada antes de dividirla entre etil acetato y agua. La capa orgánica fue separada, lavada con salmuera, secada, filtrada y concentrada *in vacuo* para obtener un sólido color café. Purificación con cromotogRafía flash con etil acetato y hexano (1:1) dió como resultado un jarabe amarillo. HPLC, 1.69 min; MH+ = 303.1.

Paso 3. Síntesis de 4-(4.metilamino-3-nitro-fenoxi)-piridin –2-ácido carboxílico dimetilamida.

Una solución de 4-(4-amino-3-nitro-fenoxi)-piridin-2-ácido carboxílico dimetilamida (1 eq) en cloruro metileno fue tratado con trifluoroacetico anhídrido (1 eq) y agitado por 10

minutos a 0° C. La mezcla fue apagada con satd solución $NaHCO_3$. La capa orgánica fu separada y lavada con agua, salmuera, secada, filtrada y evaporada. MS: MH+ = 399.0.

A una solución de trifluoroacetamida (1 eq) en una mezcla de tolueno, acetonitrilo y una solución de hidróxido de sodio (50%) fue añadido cloruro benciltrimetilamoniaco (1 eq) y sulfato dimetil (1.2 eq). La mezcla bifásica fue agitada durante la noche a temperatura ambiente. La mezcla fue tomada en etil acetato, lavada con agua, salmuera, seca, y evaporada. El producto crudo fue purificado por medio de cromatogRafía flash diluido con 5% metanol en diclorometano para obtener el producto deseado. HPLC, 2.14 min; MS: MH+ = 317.3.

Paso 4. Síntesis de 4-(3-amino-4-metilamino-fenoxi)-piridin-2-ácido carboxílico dimetilamida.

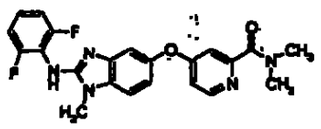
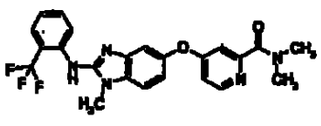
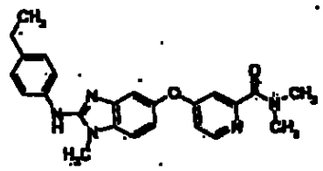
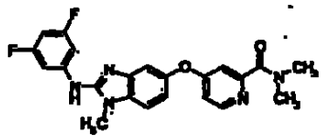
La solución de 4-(4-metilamino-3-nitro-fenoxi)-piridin-2-ácido carboxílico dimetilamida en metanol fue tratado con 10% de paladio en carbono y agitado bajo una atmósfera de hidrógeno por 3 horas a temperatura ambiente. La mezcla fue purificada con nitrógeno y luego filtrada por medio de Celite y luego el producto de la filtración fue concentrado para producir diamina. HPLC, 1.17 min; MS: MH+ = 287.1.

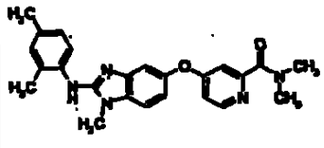
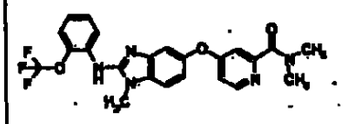
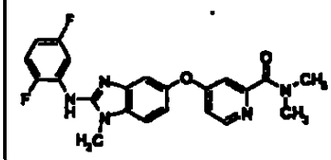
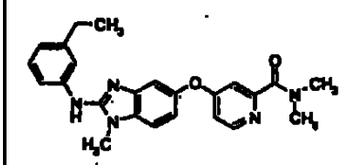
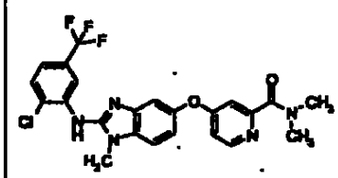
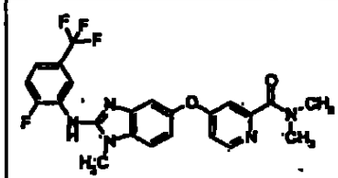
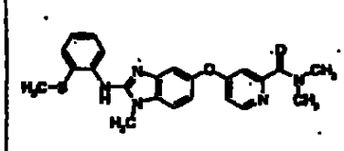
Paso 5. Síntesis de 4-[2-(2,6-difluoro-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico dimetilamida.

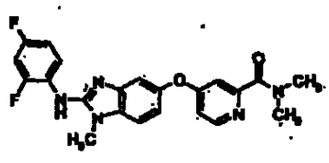
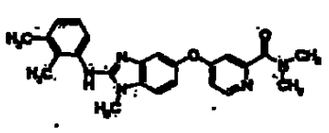
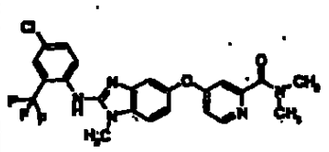
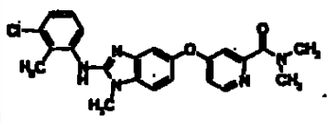
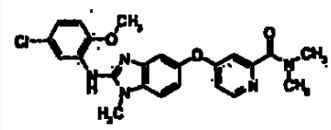
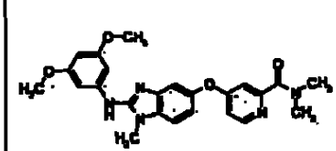
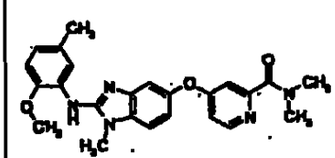
Una solución de 4-(3-amino-4-metilamino-fenoxi)-piridin-2-ácido carboxílico dimetilamida (1 eq) en metanol fue tratado con 2,6-difluorofenilisotiocianato (1 eq) y agitado durante la noche. A la mezcla de la reacción, se le añadió ioduro de metilo (1 eq) y fue agitado durante la noche a 60° C. La reacción fue enfriada a temperatura ambiente, evaporada, y el residuo purificado con HPLC fase-reversible. HPLC, 1.66 min; MS: MH+ = 424.1.

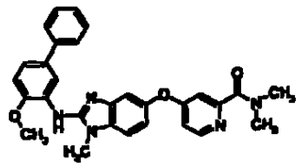
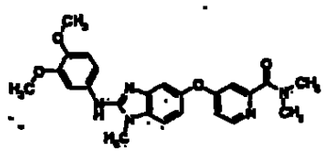
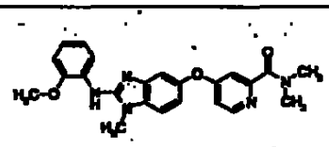
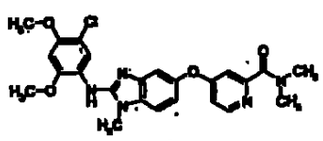
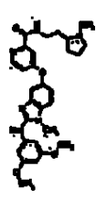
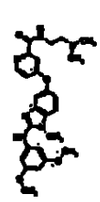
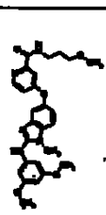
Cada uno de los compuestos 823-984 listados en la Tabla presentada a continuación, fueron sintetizados como se indicó en el método descrito en la columna derecha.

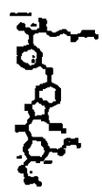
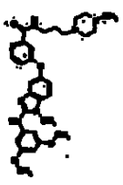
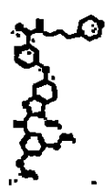
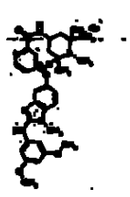
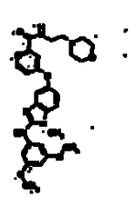
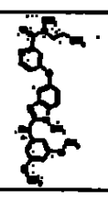
Tabla 13

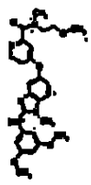
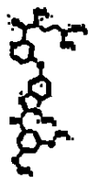
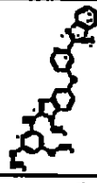
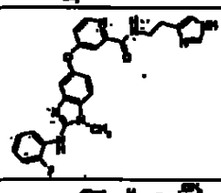
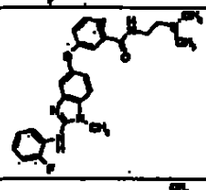
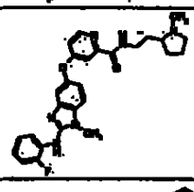
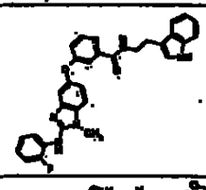
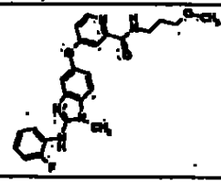
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
823		4-({2-[(2,6-difluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	424.1	822
824		N,N-dimetil-4-[(1-metil-2-{[2-(trifluorometil)fenil]-amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	456.4	822
825		4-({2-[(4-etilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	416.5	822
826		4-({2-[(3,5-difluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	424.4	822

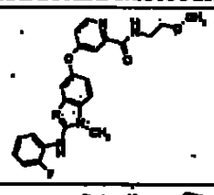
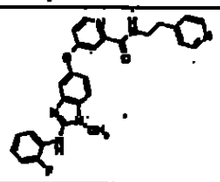
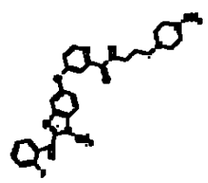
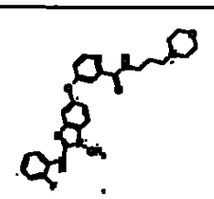
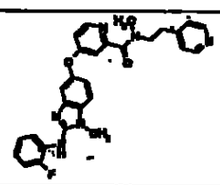
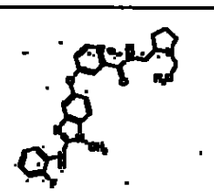
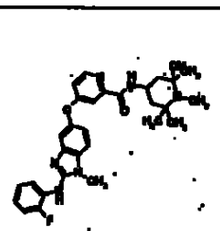
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
827		4-({2-[(2,4-dimetilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	416.5	822
828		N,N-dimetil-4-{[1-metil-2-({2-[(trifluorometil)oxi]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	472.4	822
829		4-({2-[(2,5-difluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	424.4	822
830		4-({2-[(3-etilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	416.5	822
831		4-[(2-{[2-cloro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N,N-dimetilpiridin-2-carboxamida	490.9	822
832		4-[(2-{[2-fluoro-5-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N,N-dimetilpiridin-2-carboxamida	474.4	822
833		N,N-dimetil-4-[(1-metil-2-{[2-(metiltio)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	434.5	822

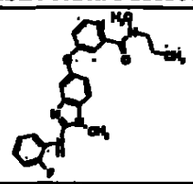
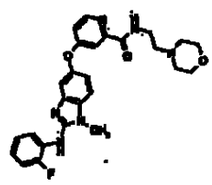
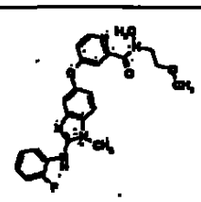
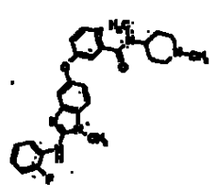
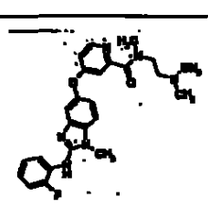
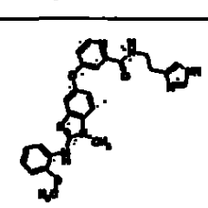
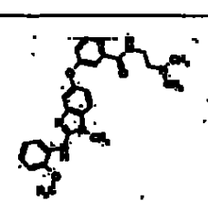
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
834		4-({2-[(2,4-difluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	424.4	822
835		4-({2-[(2,3-dimetilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	416.5	822
836		4-[(2-{[4-cloro-2-(trifluorometil)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N,N-dimetilpiridin-2-carboxamida	490.9	822
837		4-({2-[(3-cloro-2-metilfenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N,N-dimetilpiridin-2-carboxamida	436.9	822
838		4-[(2-{[5-cloro-2-(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N,N-dimetilpiridin-2-carboxamida	452.9	822
839		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N,N-dimetilpiridin-2-carboxamida	448.5	822
840		N,N-dimetil-4-[(1-metil-2-{[5-metil-2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	432.5	822

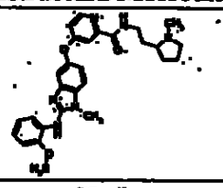
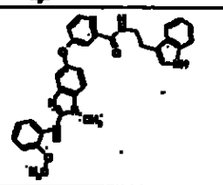
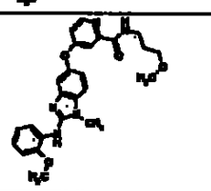
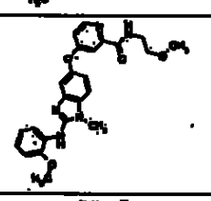
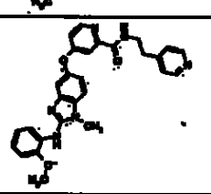
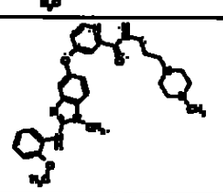
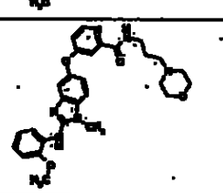
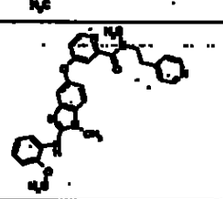
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
841		N,N-dimetil-4-[(1-metil-2-{[4-(metiloxi)-1,1'bifenil-3-il]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	494.6	822
842		4-[(2-{[3,4-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N,N-dimetilpiridin-2-carboxamida	448.5	822
843		N,N-dimetil-4-[(1-metil-2-{[2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	418.5	822
844		4-[(2-{[5-cloro-2,4-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N,N-dimetilpiridin-2-carboxamida	482.9	822
845		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(1-metilpirrolidin-2-il)etil]piridin-2-carboxamida	531.6	372
846		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(dimetilamino)etil]piridin-2-carboxamida	491.6	372
847		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(metiloxi)propil]piridin-2-carboxamida	492.5	372

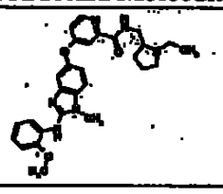
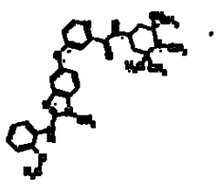
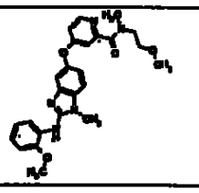
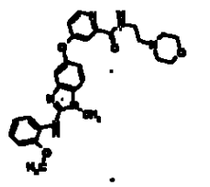
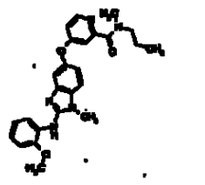
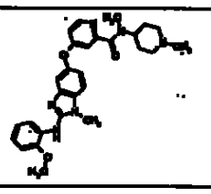
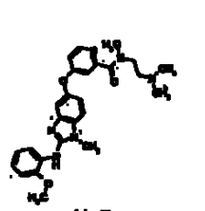
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
848		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[2-(metiloxi)propil]piridin-2-carboxamida	478.5	372
849		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(4-metilpiperazin-1-il)propil]piridin-2-carboxamida	560.7	372
850		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(3-morfolin-4-ilpropil)piridin-2-carboxamida	547.6	372
851		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(1,2,2,6,6-pentametilpiperidin-4-il)piridin-2-carboxamida	573.7	372
852		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-iletil)piridin-2-carboxamida	533.6	372
853		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metil-N-propilpiridin-2-carboxamida	476.5	372

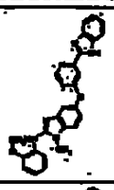
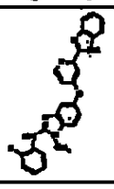
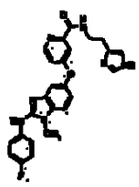
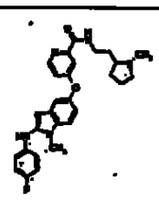
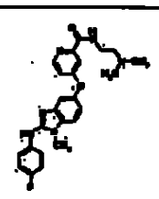
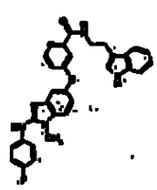
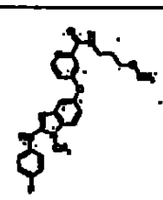
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
854		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metil-N-[2-(metiloxi)-etil]piridin-2-carboxamida	492.5	372
855		4-[(2-{[3,5-bis(metiloxi)-fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metil-N-[2-(dimetilamino)-etil]piridin-2-carboxamida	505.6	372
856		5-{[2-(1H-bencimidazol-2-il)-piridin-4-il]oxi}-N-[3,5-bis-(metiloxi)fenil]-1-metil-1H-bencimidazol-2-amina	493.5	821
857		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1H-imidazol-4-il)etil]piridin-2-carboxamida	472.5	372
858		N-[2-(dimetilamino)etil]-4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	449.5	372
859		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1-metil-pirrolidin-2-il)etil]piridin-2-carboxamida	489.6	372
860		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1H-indol-3-il)-etil]piridin-2-carboxamida	521.6	372
861		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(metiloxi)-propil]piridin-2-carboxamida	450.5	372

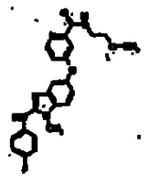
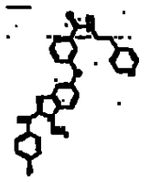
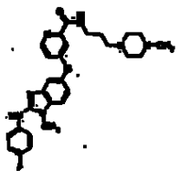
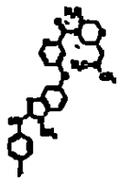
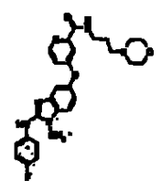
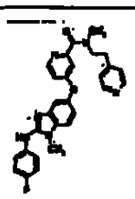
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
862		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(metiloxi)-etil]piridin-2-carboxamida	436.5	372
863		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-piridin-2-iletil)piridin-2-carboxamida	483.5	372
864		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(4-metil-piperazin-1-il)propil]piridin-2-carboxamida	518.6	372
865		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(3-morfolin-4-il-propil)piridin-2-carboxamida	505.6	372
866		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-piridin-4-iletil)piridin-2-carboxamida	497.5	372
867		N-[(1-etilpirrolidin-2-il)-metil]-4-({2-[(2-fluorofenil)-amino]-1-metil-1H-bencimidazol-5-il}oxi)piridin-2-carboxamida	489.6	372
868		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(1,2,2,6,6-penta-metilpiperidin-4-il)piridin-2-carboxamida	531.6	372

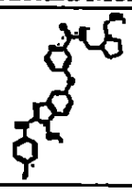
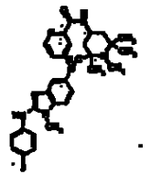
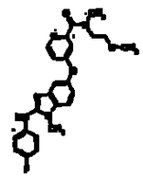
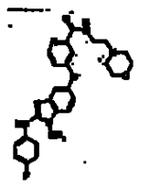
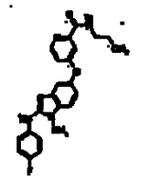
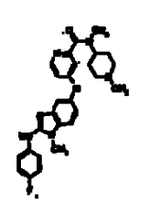
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
869		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-propil-piridin-2-carboxamida	434.5	372
870		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-morfolin-4-il-etil)piridin-2-carboxamida	491.5	372
871		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-[2-(metil-oxi)etil]piridin-2-carboxamida	450.5	372
872		4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-(1-metil-piperidin-4-il)piridin-2-carboxamida	489.6	372
873		N-[2-(dimetilamino)etil]-4-({2-[(2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	463.5	372
874		N-[2-(1H-imidazol-4-il)etil]-4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	484.5	372
875		N-[2-(2H(dimetilamino)etil]-4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	461.5	372

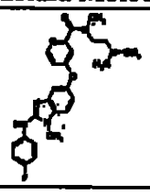
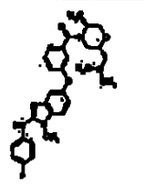
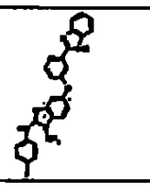
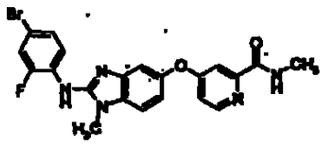
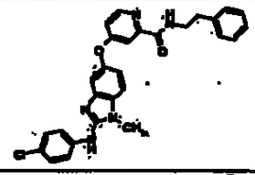
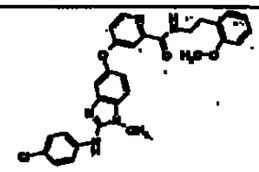
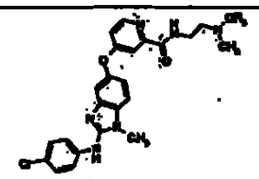
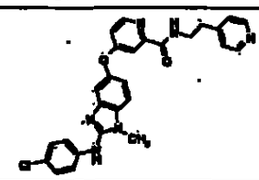
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
876		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-[2-(1-metilpirrolidin-2-il)etil]-piridin-2-carboxamida	501.6	372
877		N-[2-(1H-indol-3-il)etil]-4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	533.6	372
878		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-[3-(metiloxi)propil]-piridin-2-carboxamida	462.5	372
879		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-[2-(metoxi)etil]-piridin-2-carboxamida	448.5	372
880		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-piridin-4-iletil)piridin-2-carboxamida	495.6	372
881		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-[3-(4-metilpiperazin-1-il)propil]-piridin-2-carboxamida	530.6	372
882		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(3-morfolin-4-ilpropil)piridin-2-carboxamida	517.6	372
883		N-metil-4-[(1-metil-2-{[2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-piridin-4-iletil)piridin-2-carboxamida	509.6	372

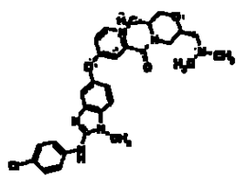
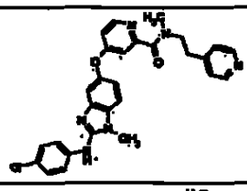
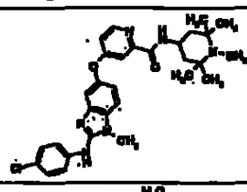
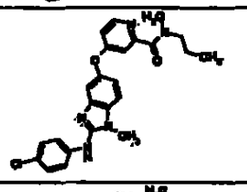
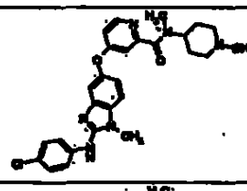
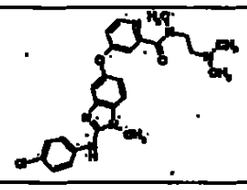
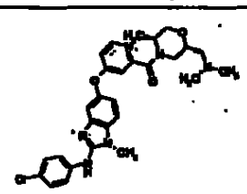
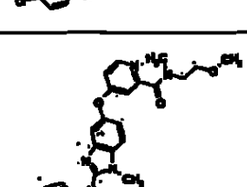
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
884		N-[(1-etilpirrolidin-2-il)-metil]-4-[(1-metil-2-{[2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	501.6	372
885		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(1,2,2,6,6-pentametilpiperidin-4-il)piridin-2-carboxamida	543.7	372
886		N-metil-4-[(1-metil-2-{[2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]N-[2-(metiloxi)etil]piridin-2-carboxamida	462.5	372
887		4-[(1-metil-2-{[2-(metiloxi)-fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-iletil)piridin-2-carboxamida	503.6	372
888		N-metil-4-[(1-metil-2-{[2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]N-propilpiridin-2-carboxamida	446.5	372
889		N-metil-4-[(1-metil-2-{[2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]N-(1-metilpiperidin-4-il)piridin-2-carboxamida	501.6	372
890		N-[2-(dimetilamino)etil]-N-metil-4-[(1-metil-2-{[2-(metiloxi)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	475.6	372

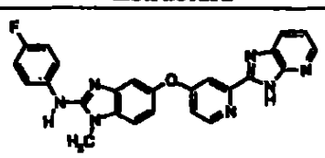
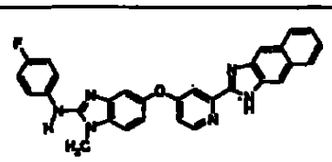
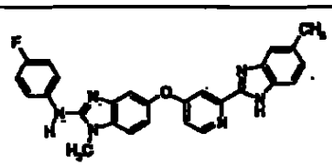
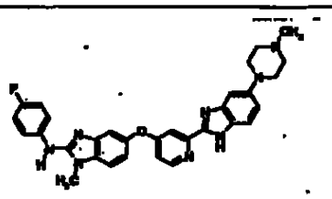
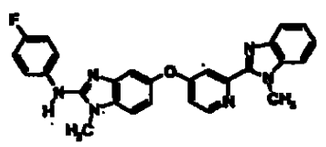
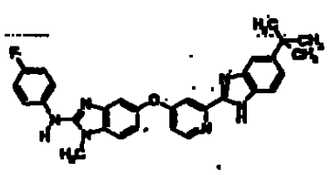
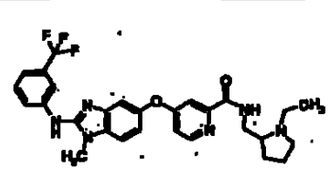
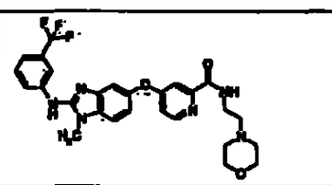
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
891		5-{[2-(1H-bencimidazol-2-il)piridin-4-il]oxi}-1-metil-N-[2-(metiloxi)fenil]-1H-bencimidazol-2-amina	463.5	372
892		5-{[2-(1H-bencimidazol-2-il)piridin-4-il]oxi}-N-(2-fluorofenil)-1-metil-1H-bencimidazol-2-amina	451.5	372
893		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1H-imidazol-4-il)etil]piridin-2-carboxamida	472.5	372
894		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1-metil-pirrolidin-2-il)etil]piridin-2-carboxamida	489.6	372
895		N-[2-(dimetilamino)etil]-4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}-oxi)piridin-2-carboxamida	449.6	372
896		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(1H-indol-3-il)-etil]piridin-2-carboxamida	521.6	372
897		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(metiloxi)-propil]piridin-2-carboxamida	450.5	372

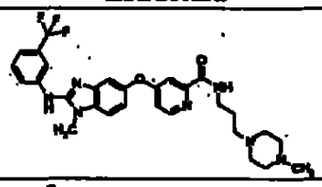
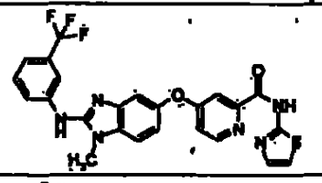
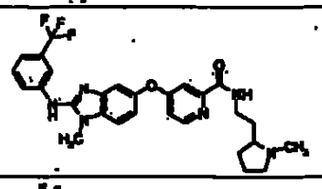
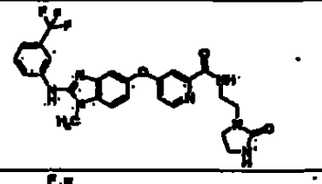
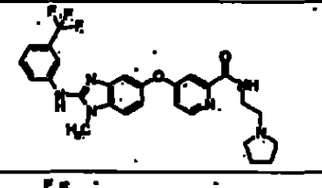
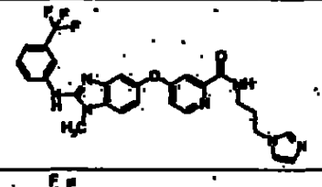
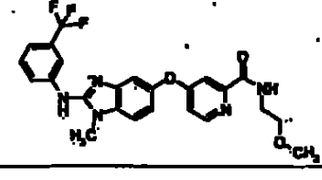
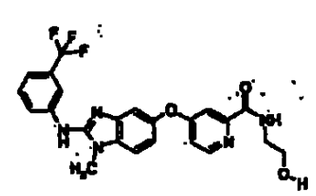
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
898		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(metiloxi)-etil]piridin-2-carboxamida	436.5	372
899		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-piridin-4-iletil)-piridin-2-carboxamida	483.6	372
900		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[3-(4-metil-piperazin-1-il)propil]piridin-2-carboxamida	518.6	372
901		5-{[2-({(2R,5R)-2-[(dimetil-amino)metil]-5-metil-morfolin-4-il}carbonil)-piridin-4-il]oxi}-N-(4-fluoro-fenil)-1-metil-1H-bencimidazol-2-amina	519.6	371
902		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(3-morfolin-4-il-propil)-piridin-2-carboxamida	505.6	372
903		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-(2-piridin-4-iletil)piridin-2-carboxamida	497.6	372

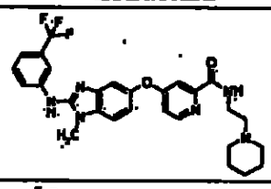
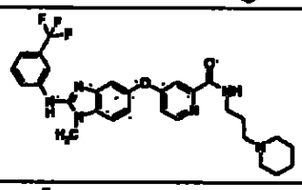
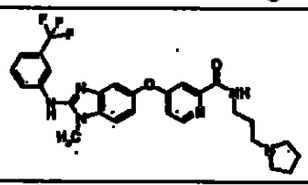
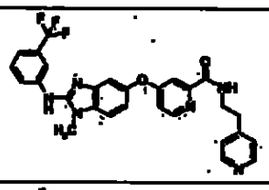
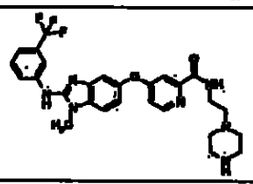
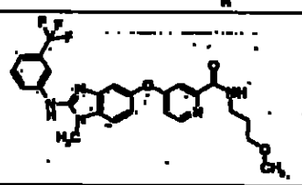
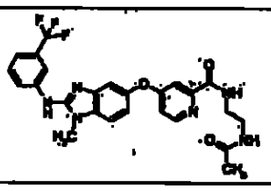
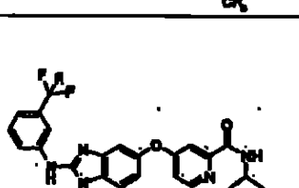
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
904		N-[(1-etilpirrolidin-2-il)-metil]-4-({2-[(4-fluoro-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	489.6	372
905		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(1,2,2,6,6-penta-metilpiperidin-4-il)-piridin-2-carboxamida	531.7	372
906		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-[2-(metiloxi)etil]piridin-2-carboxamida	450.6	372
907		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-morfolin-4-il-etil)-piridin-2-carboxamida	491.6	372
908		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-propilpiridin-2-carboxamida	434.6	372
909		4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-(1-metil-piperidin-4-il)piridin-2-carboxamida	489.6	372

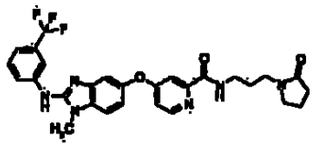
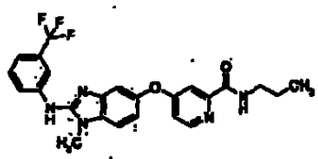
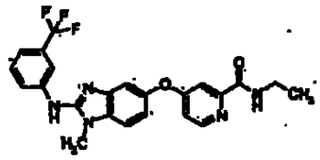
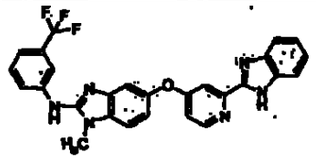
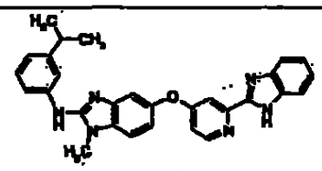
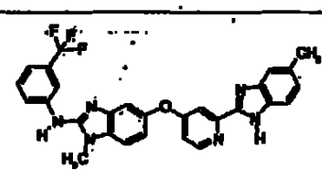
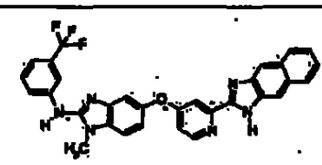
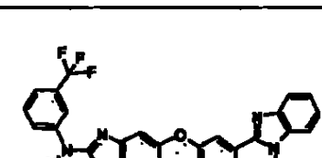
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
910		N-[2-(dimetilamino)etil]-4-({2-[(4-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}-oxi)-N-metilpiridin-2-carboxamida	463.6	372
911		5-{[2-({(2R,5S)-2-[(dimetil-amino)metil]-5-metil-morfolin-4-il}carbonil)-piridin-4-il]oxi}-N-(4-fluoro-fenil)-1-metil-1H-bencimidazol-2-amina	519.6	372
912		5-{[2-(1H-bencimidazol-2-il)piridin-4-il]oxi}-N-(4-fluorofenil)-1-metil-1H-bencimidazol-2-amina	451.5	821
913		4-({2-[(4-bromo-2-fluorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	471.3	120a
914		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-feniletil)-piridin-2-carboxamida	499.0	392
915		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-{2-[2-(metiloxi)-fenil]etil}piridin-2-carboxamida	529.0	372
916		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(dimetilamino)-etil]-piridin-2-carboxamida	466.0	372
917		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-piridin-4-iletil)-piridin-2-carboxamida	500.0	37

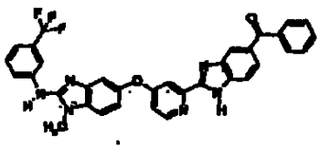
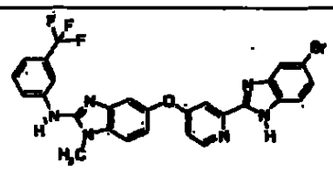
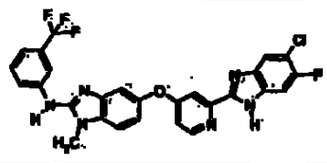
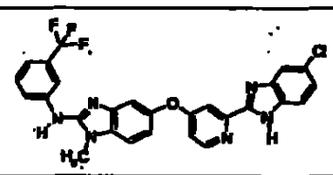
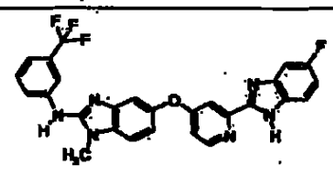
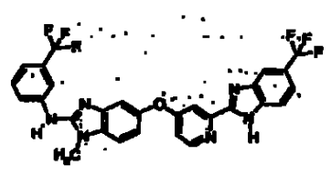
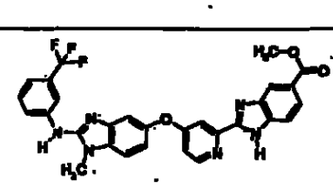
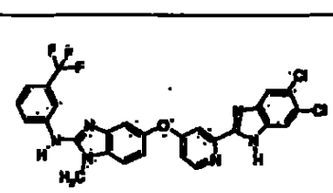
Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
918		N-(4-clorofenil)-5-{[2-({(2R,5R)-2-[(dimetilamino)-metil]-5-metilmorfolin-4-il}carbonil)piridin-4-il]oxi}-1-metil-1H-bencimidazol-2-amina	536.0	372
919		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-(2-piridin-4-iletil)piridin-2-carboxamida	514.0	372
920		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(1,2,2,6,6-penta-metilpiperidin-4-il)piridin-2-carboxamida	548.1	372
921		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-propil-piridin-2-carboxamida	450.9	372
922		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-(1-metil-piperidin-4-il)piridin-2-carboxamida	506.0	372
923		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-[2-(dimetilamino)-etil]-N-metilpiridin-2-carboxamida	480.0	372
924		N-(4-clorofenil)-5-{[2-({(2R,5S)-2-[(dimetilamino)-metil]-5-metilmorfolin-4-il}carbonil)piridin-4-il]oxi}-1-metil-1H-bencimidazol-2-amina	536.0	372
925		4-({2-[(4-clorofenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-metil-N-[2-(metiloxi)etil]piridin-2-carboxamida	466.9	372

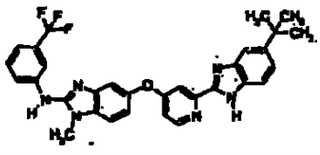
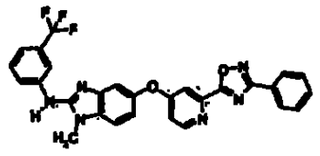
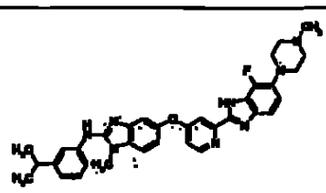
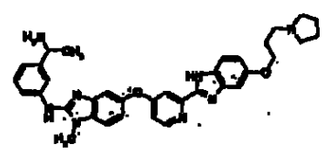
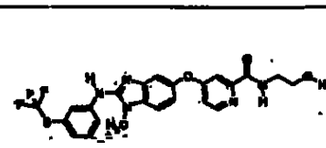
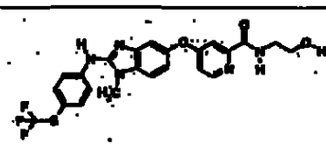
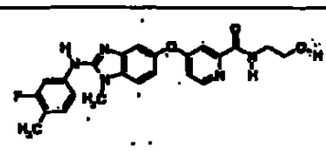
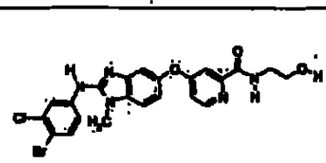
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
926		N-(4-fluorofenil)-5-{[2-(3H-imidazol[4,5-b]piridin-2-il)-piridin-4-il]oxi}-1-metil-1H-bencimidazol-2-amina	452.5	821
927		N-(4-fluorofenil)-1-metil-5-{[2-(1H-nafto[2,3-d]-imidazol-2-ionil)piridin-4-il]oxi}-1H-bencimidazol-2-amina	501.5	821
928		N-(4-fluorofenil)-1-metil-5-{[2-(5-metil-1H-bencimidazol-2-il)piridin-4-il]oxi}-1H-bencimidazol-2-amina	465.5	821
929		N-(4-fluorofenil)-1-metil-5-({2-[5-(4-metilpiperazin-1-il)-1H-bencimidazol-2-il]piridin-4-il}oxi)-1H-bencimidazol-2-amina	549.6	821
930		N-(4-fluorofenil)-1-metil-5-{[2-(1-metil-1H-bencimidazol-2-il)piridin-4-il]oxi}-1H-bencimidazol-2-amina	465.5	821
931		5-({2-[5-(1,1-dimetiletil)-1H-bencimidazol-2-il]piridin-4-il}oxi)-N-(4-fluorofenil)-1-metil-1H-bencimidazol-2-amina	507.6	821
932		N-[(1-etilpirrolidin-2-il)-metil]-4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	539.3	372
933		4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-iletil)piridin-2-carboxamida	541.3	372

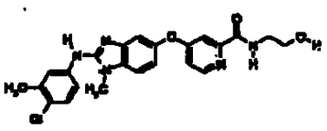
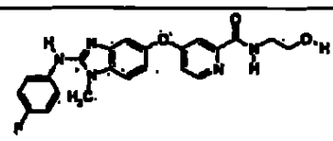
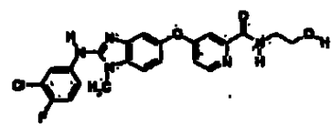
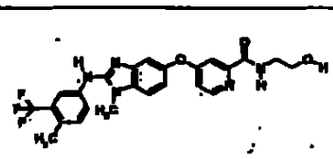
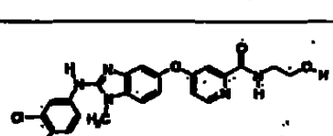
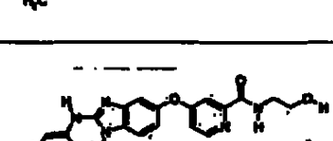
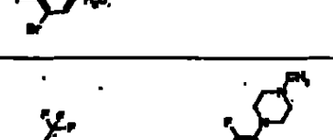
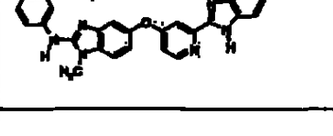
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
934		N-[3-(4-metilpiperazin-1-il)-propil]-4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	568.4	372
935		4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-1,3-tiazol-2-ilpiridin-2-carboxamida	511.2	372
936		N-[2-(1-metilpirrolidin-2-il)-etil]-4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	539.3	372
937		4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-[2-(2-oxoimidazolidin-1-il)etil]-piridin-2-carboxamida	540.3	372
938		4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-pirrolidin-1-iletil)piridin-2-carboxamida	525.3	372
939		N-[3-(1H-imidazol-1-il)propil]-4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	536.3	372
940		N-[2-(metiloxi)etil]-4-[(1-metil-2-{[3-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboximida	486.3	372
941		N-(2-hidroxietil)-4-[(1-metil-2-{[3-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	472.2	372

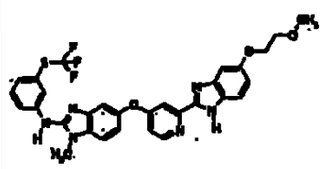
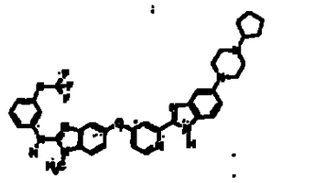
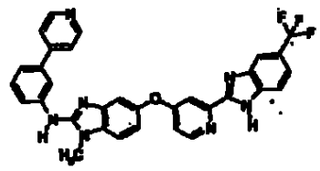
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
942		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-piperidin-1-iletil)piridin-2-carboxamida	539.3	372
943		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(3-piperidin-1-ilpropil)piridin-2-carboxamida	553.3	372
944		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(3-pirrolidin-1-ilpropil)piridin-2-carboxamida	539.3	372
945		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-piridin-4-iletil)piridin-2-carboxamida	533.3	372
946		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-(2-piperazin-1-iletil)piridin-2-carboxamida	540.2	372
947		N-[3-(metiloxi)propil]-4-[(1-metil-2-{[3-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboximida	500.2	372
948		N-[2-(acetilamino)etil]-4-[(1-metil-2-{[3-(trifluorometil)-fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	513.3	372
949		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-pirrolidin-3-ilpiridin-2-carboxamida	497.2	372

Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
950		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-[3-(2-oxopirrolidin-1-il)propil]-piridin-2-carboxamida	553.3	372
951		4-[(1-metil-2-{[3-(trifluoro-metil)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-propilpiridin-2-carboxamida	470.3	372
952		N-etil-4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	456.2	372
953		5-{[2-(1H-bencimidazol-2-il)piridin-4-il]oxi}1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	501.2	821
954		5-{[2-(1H-bencimidazol-2-il)piridin-4-il]oxi}1-1metil-N-[3-(1-metiletil)fenil]-1H-bencimidazol-2-amina	abran	821
955		1-metil-5-{[2-(5-metil-1H-bencimidazol-2-il)piridin-4-il]oxi}-N-[3-(trifluorometil)-fenil]-1H-bencimidazol-2-amina	515.2	821
956		1-metil-5-{[2-(1H-nafto[2,3-d]imidazol-2-il)piridin-4-il]oxi}-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	551.3	821
957		1-metil-5-{[2-(1-metil-1H-bencimidazol-2-il)piridin-4-il]oxi}-N-[3-(trifluorometil)-fenil]-1H-bencimidazol-2-amina	515.2	821

Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
958		(2-{4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]-piridin-2-il}-1H-bencimidazol-5-il)(fenil)metanona	605.2	821
959		5-{[2-(5-bromo-1H-bencimidazol-2-il)piridin-4-il]oxi}1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	579.1	821
960		5-{[2-(5-cloro-6-fluoro-1H-bencimidazol-2-il)piridin-4-il]oxi}1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	553.2	821
961		5-{[2-(5-cloro-1H-bencimidazol-2-il)piridin-4-il]oxi}1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	535.2	821
962		5-{[2-(5-fluoro-1H-bencimidazol-2-il)piridin-4-il]oxi}1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	519.4	821
963		1-metil-5-({2-[5-(trifluorometil)-1H-bencimidazol-2-il]piridin-4-il}oxi)-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	569.2	821
964		Metil 2-{4-[(1-metil-2-{[3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-il}-1H-bencimidazol-5-carboxilato	559.2	821
965		5-{[2-(5,6-dicloro-1H-bencimidazol-2-il)piridin-4-il]oxi}1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	569.1	821

Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
966		5-({2-[5-(1,1-dimetiletil)-1H-bencimidazol-2-il]piridin-4-il}oxi)-1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	557.3	821
967		1-metil-5-{[2-(3-fenil-1,2,4-oxadiazol-5-il)piridin-4-il]oxi}-N-[3-(trifluorometil)-fenil]-1H-bencimidazol-2-amina	529.2	821
968		5-({2-[7-fluoro-6-(4-metil-piperazin-1-il)-1H-bencimidazol-2-il]piridin-4-il}oxi)-1-metil-N-[3-(1-metiletil)fenil]-1H-bencimidazol-2-amina	591.3	821
969		1-metil-N-[3-(1-metil-etil)fenil]-5-[(2-{5-[(3-pirrolidin-1-ilpropil)oxi]-1H-bencimidazol-2-il}piridin-4-il)oxi]-1H-bencimidazol-2-amina	602.7	821
970		N-(2-hidroxietil)-4-{[1-metil-2-({3-[(trifluorometil)-tio]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	504.1	820
971		N-(2-hidroxietil)-4-{[1-metil-2-({4-[(trifluorometil)-tio]fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	504.1	820
972		4-({2-[(3-fluoro-4-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-hidroxietil)piridin-2-carboxamida	436.2	820
973		4-({2-[(4-bromo-3-cloro-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-hidroxietil)piridin-2-carboxamida	516	820

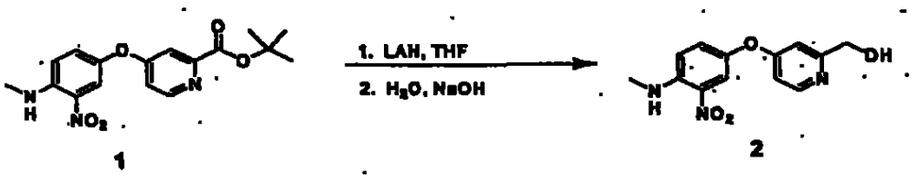
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
974		4-({2-[(4-cloro-3-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-hidroxietil)piridin-2-carboxamida	452.2	820
975		4-({2-[(4-fluorometil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-hidroxietil)piridin-2-carboxamida	422.2	820
976		4-({2-[(3-cloro-4-fluoro-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-hidroxietil)piridin-2-carboxamida	456.2	820
977		N-(2-hidroxietil)-4-[(1-metil-2-{[4-metil-3-(trifluorometil)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	486.2	820
978		4-({2-[(3-cloro-4-metil-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-hidroxietil)piridin-2-carboxamida	452.2	820
979		4-({2-[(4-bromo-3-fluoro-fenil)amino]-1-metil-1H-bencimidazol-5-il}oxi)-N-(2-hidroxietil)piridin-2-carboxamida	502.1	820
980		5-({2-[4-fluoro-5-(4-metil-piperazin-1-il)-1H-bencimidazol-2-il]piridin-4-il}oxi)-1-metil-N-[3-(trifluorometil)fenil]-1H-bencimidazol-2-amina	428.2	821
981		5-{[2-(1H-bencimidazol-2-il)-piridin-4-il]oxi}-N-(4-cloro-3-piridin-4-ilfenil)-1-metil-1H-bencimidazol-2-amina	545.0	821

Ejemplo	Estructura Molecular	Nombre	MH+	Sintetizado como en el ejemplo
982		1-metil-5-{[2-(5-{[2-(metil-oxi)etil]oxi}-1H-bencimidazol-2-il)piridin-4-il]oxi}-1-{3-[(trifluorometil)tio]-fenil}-1H-bencimidazol-2-amina	607.2	821
983		5-({2-[5-(4-ciclopentil-piperazin-1-il-)-1H-bencimidazol-2-il]piridin-4-il}oxi)1-metil-N-{3-[(trifluorometil)tio]fenil}-1H-bencimidazol-2-amina	685.3	821
984		1-metil-N-(3-piridin-4-il-fenil)-5-({2-[5-(trifuorometil)-1H-bencimidazol-2-il]piridin-4-il}oxi)-1H-bencimidazol-2-amina	578.3	821

Ejemplo 985:

Síntesis de series de oxima: 4-[2-(4-Bromo-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-carbaldehida oxima

Paso 1. Síntesis de [4-(4-Metilamino-3-nitro-fenoxi)-piridin-2-il]-metanol

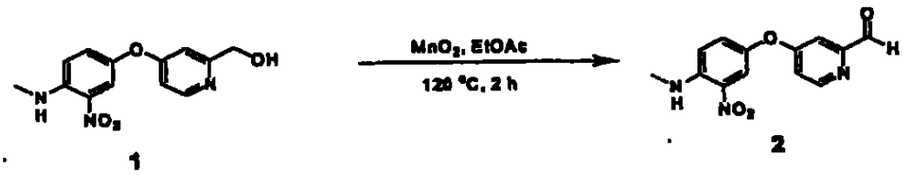


1 2

Un frasco con tres cuellos de fondo redondo secado con llama purificado con N_2 fue cargado con LAH (2.32 g , 58.0 mmol) y THF seco (60mL). La suspensión resultante fue enfriada a 0° C y una suspensión de *t*-butil ester 1 (10.0g, 29.0 mmol) en THF seco (60 mL) fue añadida lentamente mientras la temperatura de la reacción interna fue mantenida a 5° C.

La reacción fue agitada a 0° C por 30 minutos y luego a temperatura ambiente por 30 minutos. Luego de que la reacción fue completa, la mezcla fue tratada con adiciones sucesivas de gotas de agua (2.3 mL), 10% NaOH (2.3 mL), y agua (7.2 mL). La suspensión resultante fue filtrada por medio de Celite, lavada con etil acetato y metanol, y los orgánicos concentrados recolectados. El producto crudo fue absorbido en Silica gel y purificado por cromatogRafía flash. (97:3 CH_2Cl_2/MeOH) para dar **2** como un sólido anaranjado: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J*= 5.5 Hz, 1 H), 8.05 (br s, 1H), 7.96 (d, *J*= 2.75 Hz, 1 H), 6.92 (d, *J*= 9.35 Hz, 1 H), 6.75 (m, 2 H), 4.68 (s, 2 H), 3.07 (d, *J*= 5.23 Hz, 3 H).

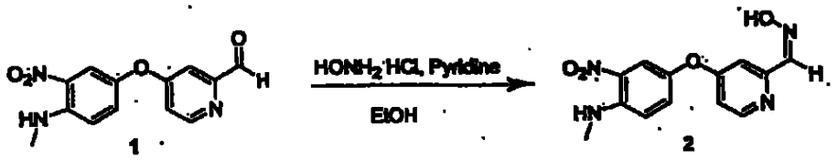
Paso 2. Síntesis de 4-(4-Metilamino-3-nitro-fenoxi)-piridin-2-carbaldehida



1 2

Un tubo reactor de 250 mL fue cargado con alcohol bencil **1** (1.0 g, 3.6 mmol), MnO_2 (4.7 g, 54 mmol) y EtOAc (20 mL). El tubo reactor fue sellado y calentado a 120° C con agitación por 2 horas. La reacción fue dejada enfriar a temperatura ambiente, luego filtrada por medio de Celite, y lavada sucesivamente con EtOAc, MeOH, y EtOH. Los orgánicos combinados fueron concentrados para dar como resultado 936 mg (3.4 mmol, 94%) de **2** como un sólido anaranjado: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1 H), 8.64 (d, *J*= 5.5 Hz, 1 H), 8.09 (br s, 1H), 7.96 (d, *J*= 2.75 Hz, 1 H), 7.37 (d, *J*= 2.48 Hz, 1 H), 7.29 (d, *J*= 2.72 Hz, 1 H), 7.08 (dd, *J*= 2.47, 5.5 Hz, 1 H), 6.94 (d, *J*= 9.35 Hz, 1 H), 3.08 (d, *J*= 5.23 Hz, 3 H).

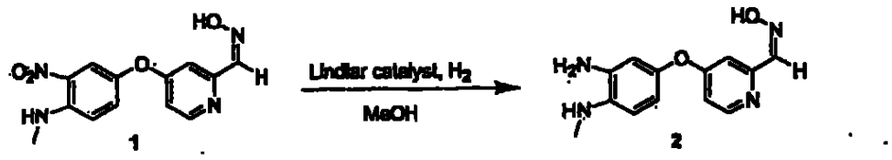
Paso 3. Síntesis de 4-(4-Metilamino-3-nitro-fenoxi)-piridin-2-carbaldehida oxima.



1 2

Un frasco de fondo redondo de 50 mL fue cargado con 1 (680 mg, 2.5 mmol), HCl hidroxiamina (191 mg, 2.75 mmol), piridina (0.25 mL, 3.0 mmol) y etanol (10 mL). La mezcla de la reacción resultante fue agitada a temperatura ambiente durante la noche. El producto crudo fue concentrado, absorbido en silica gel, y purificado por cromatogRafía flash (97:3 CH_2Cl_2/MeOH) para dar 2 como un sólido anaranjado. LCMS *m/z* 289.2 (MH^+), t_R = 2.06 min.

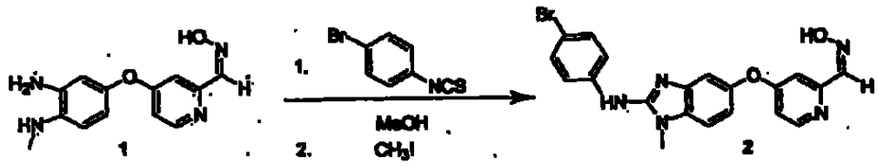
Paso 4. Síntesis de 4-(3-Amino-4-metilamino-fenoxi)piridin-2-carbaldehida oxima



1 2

El tubo reactor fue cargado con suspensión de 1 (330 mg, 1.15 mmol) y catalizador Lindlar (245 mg, 10 mol %) en metanol (5 mL), sellado, y puesto en un sacudidor Parrr. La reacción fue presurizada con H_2 (60 psi) y mantenida por una hora. La reacción fue filtrada por medio de Celite y los sólidos resultantes fueron lavados con MeOH. Los orgánicos combinados fueron concentrados para dar 2 como un semi-sólido café que fue tomado sin purificación adicional.

Paso 5. Síntesis de 4-[2-(4-Bromo-fenilamino)-1-metil-1H-bencimidazol-5-iloxi]-piridin-2-carbaldehido oxima

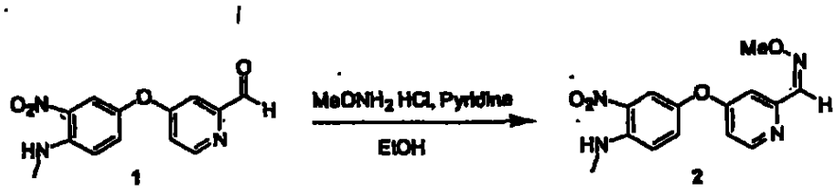


Un frasco de base redonda fue cargado con 4-Bromofenilisiotiocianato (54 mg, 0.25 mmol), diamina 1 (65 mg, 0.25 mmol), y MeOH (1 mL). La reacción resultante fue mantenida a temperatura ambiente durante la noche. Ioduro de metilo (20 µL, 0.33 mmol) fue añadido a la reacción y agitado durante la noche. La reacción fue concentrada y el residuo resultante fue purificado por HPLC fase-reversiva. LCMS *m/z* 438.1 (MH^+), t_R = 1.87 min.

Ejemplo 986

Síntesis de serie *O*-metil-oxima: 4-[1-Metil-2-(4-trifluorometilsulfanil-fenilamino)-1H-benzoimidazol-5-iloxi]-piridin-2-carbaldehida *O*-metil-oxima

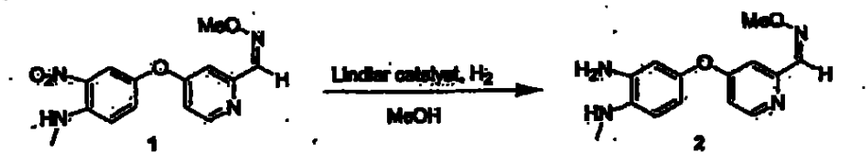
Paso 1. Síntesis de 4-(4-Metilamino-3-nitro-fenoxi)-piridin-2-carbaldehida *O*-metil-oxima



Un frasco de base redonda de 25 mL cargado con una suspensión de 1 (600 mg, 2.2 mmol), HCl metoxilamina (202 mg, 2.42 mmol) y piridin (0.22 mL, 2.6 mmol) en etanol (9 mL). La mezcla de la reacción resultante fue agitada a temperatura ambiente durante la noche. El producto crudo fue concentrado, absorbido en silica gel, y purificado por cromatogRafía flash (97:3 CH_2Cl_2/MeOH) para dar 2 como un sólido anaranjado. LCMS *m/z* 303.2 (MH^+), t_R = 2.40 min.

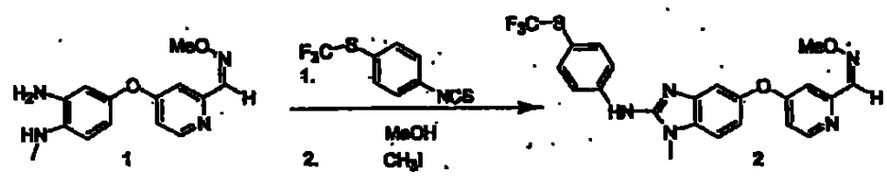
372

Paso 2. Síntesis de 4-(3-Amino-4-metilamino-fenoxi)-piridin-2-carbaldehide *O*-metil-oxima



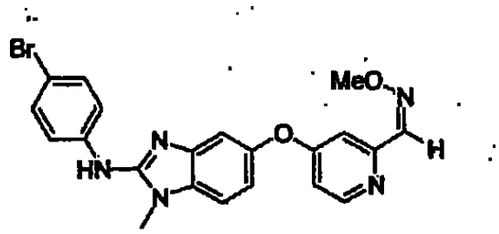
Un tubo reactor fue cargado con una suspensión de 1 (270 mg, 0.9 mmol) y un catalizador Lindlar (192 mg, 10 mol %) en metanol (5 mL), y luego fue puesto en un sacudidor Parr. La reacción fue presurizada con H_2 (60 psi) y mantenida por una hora. La reacción fue filtrada por medio de Celite y los sólidos resultantes fueron lavados con metanol. Los orgánicos combinados fueron concentrados para dar 2 como un semi-sólido café que fue tomado sin purificación adicional. LCMS *m/z* 273.3 (MH^+), t_R = 1.56 min.

Paso 3. Síntesis de 4-[1-Metil-2-(4-trifluorometilsulfanil-fenilamino-1H-benzoimidazol-5-iloxi)-piridin-2-carbaldehida *O*-metil-oxima



Un frasco de base redonda de 5 mL fue cargado con 4-trifluorometiltio-fenilisiotiocianato (24 mg, 0.1 mmol), diamina 1 (27 mg, 0.1 mmol), y MeOH (0.5 mL). La reacción fue mantenida a temperatura ambiente durante la noche, y luego se le añadió ioduro de metilo (8 µL, 0.13 mmol). Luego de 16 horas, la reacción fue concentrada y los residuos resultantes fueron purificados por HPLC fase-reversiva. LCMS *m/z* 474.3 (MH^+), t_R = 2.42 min.

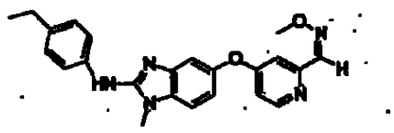
Ejemplo 987



Sintetizado como descrito en el Ejemplo 986 Paso 3 usando 4-bromofenilisiotiocianato.

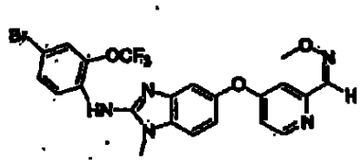
LCMS *m/z* 402.4 (MH^+), t_R = 2.15 min.

Ejemplo 988



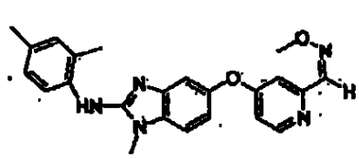
Sintetizado como descrito en el Ejemplo 986 Paso 3 usando 4-etilfenilisiotiocianato. LCMS *m/z* 402.4 (MH^+), t_R = 2.15 min.

Ejemplo 989



Sintetizado como descrito en el Ejemplo 986 Paso 3 usando 4-bromo-2-trifluorometilfenilisiotiocianato. LCMS *m/z* 536.2 (MH^+), t_R = 2.38 min.

Ejemplo 990

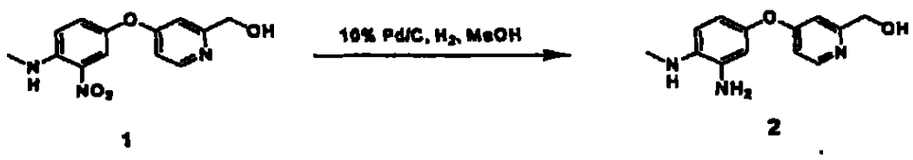


Sintetizado como descrito en el Ejemplo 986 Paso 3 usando 2,4-dimetilfenilisiotiocianato. LCMS *m/z* 402 (MH^+), t_R = 2.07 min.

Ejemplo 991

Síntesis de serie Bencil Alcohol: {4-[2-(4-Cloro-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-il}-metanol

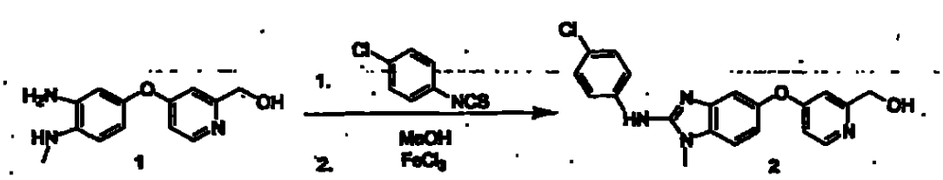
Paso 1. Síntesis de [4-(3-Amino-4-metilamino-fenoxi)-piridin-2-il]-metanol



1 2

Una suspensión de nitroanilina 1 (550 mg, 2.0 mmol) en metanol fue soplada con N_2 por 20 minutos y luego se le añadió 10% Pd/C (106 mg, 0.1mmol). La reacción fue cargada con H_2 y mantenida bajo una atmósfera de H_2 durante la noche a temperatura ambiente. La reacción fue soplada con N_2 y filtrada por medio de Celite. Los sólidos recolectados fueron lavados con EtOAc (3 X 50 mL), y las capas orgánicas combinadas fueron secadas ($MgSO_4$) y concentradas para crear 2, que fue tomado sin purificación adicional.

Paso 2. Síntesis de {4-[2-(4-Cloro-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-il}-metanol.

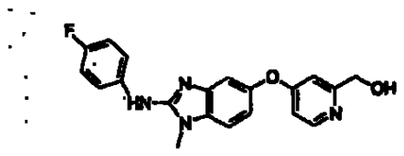


1 2

Un frasco de base redonda de 5 mL fue cargado con 4-clorofenilisotiocianato (34 g, 0.2 mmol), diamina 1 (49 mg, 0.2 mmol), y MeOH (1 mL) y la reacción resultante fue mantenida a temperatura ambiente durante la noche. Cloruro férrico (16 mg, 0.1 mmol) fue añadido y la

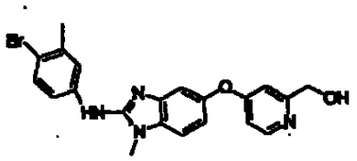
mezcla roja de la reacción fue agitada durante la noche. La reacción fue separada con EtOAc y agua, las capas fueron separadas y la fase acuosa fue neutralizada (pH = 7) con una solución acuosa saturada de Na_2CO_3. La fase acuosa fue extraida con EtOAc. Las capas orgánicas combinadas fueron lavadas con agua salada, secadas, y concentradas para dar como resultado un sólido café. La reacción fue concentrada y el residuo resultante purificado en HPLC fase-reversiva. LCMS *m/z* 381.3 (MH^+), t_R = 2.27 min.

Ejemplo 992



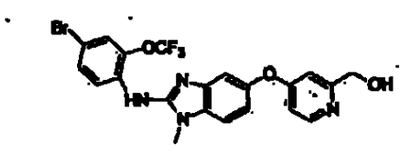
Sintetizado como descrito en el Ejemplo 1058 Paso 2 usando 4-fluorofenilisiotiocianato. LCMS *m/z* 365.4 (MH^+), t_R = 2.04 min.

Ejemplo 993



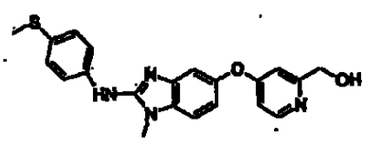
Sintetizado como descrito en el Ejemplo 991 Paso 2 usando 4-bromo-3-metilfenilisiotiocianato. LCMS *m/z* 439.3 (MH^+), t_R = 2.79 min.

Ejemplo 994



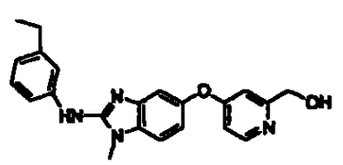
Sintetizado como descrito en el Ejemplo 991 Paso 2 usando 4-bromo-2-trifluorometoxifenilisotiocianato. LCMS *m/z* 511.3 (MH^+), t_R = 3.08 min.

Ejemplo 995



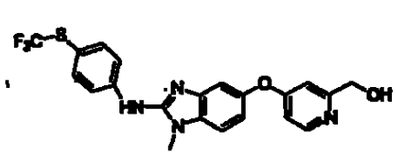
Sintetizado como descrito en el Ejemplo 991 Paso 2 usando 4-metiltiofenilisiotiocianato. LCMS *m/z* 393.4 (MH^+), t_R = 2.46 min.

Ejemplo 995



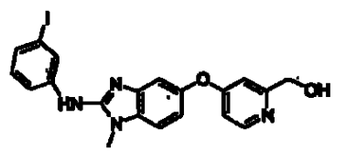
Sintetizado como descrito en el Ejemplo 991 Paso 2 usando 3-etilfenilisiotiocianato. LCMS *m/z* 375.4 (MH^+), t_R = 2.57 min.

Ejemplo 996



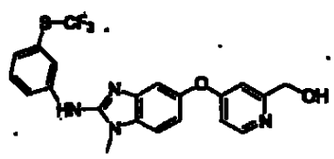
Sintetizado como descrito en el Ejemplo 991 Paso 2 usando 4-trifluorometiltio-fenilisiotiocianato. LCMS *m/z* 447.3 (MH^+), t_R = 3.21 min.

Ejemplo 997



Sintetizado como descrito en el Ejemplo 991 Paso 2 usando 3-iodofenilisiotiocianato. LCMS *m/z* 473.2 (MH^+), t_R = 2.57 min.

Ejemplo 998



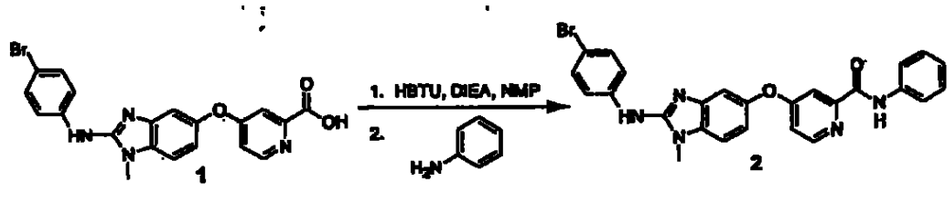
Sintetizado como descrito en el Ejemplo 991 Paso 2 usando 3-trifluorometiltiofenilisotiocianato. LCMS *m/z* 447.3 (MH^+), t_R = 3.08 min.

Ejemplo 999

4-[2-(4-Bromo-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico fenilamida

Procedimiento para la Síntesis de la Serie Anilida (4-Br y 3-iPr west-ends)

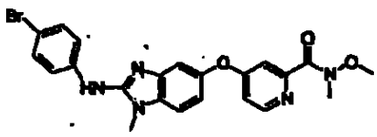
Síntesis de 4-[2-(4-Bromo-fenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico fenilamina.



Una suspensión de 1 (44 mg, 0.1 mmol), HBTUB (46 mg, 0.12 mmol) y DIEA (43 uL, 0.25 mmol) en NMP (0.5 mL) fue sacudida por 30 minutos a temperatura ambiente. Anilina

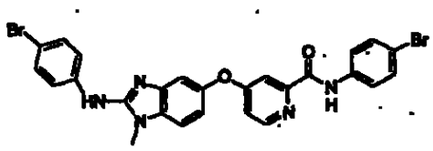
fue añadida y la reacción fue sacudida durante la noche. El producto crudo fue purificado en HPLC fase-reversiva. LCMS *m/z* 515.2 (MH^+), t_R = 2.75 min.

Ejemplo 1000



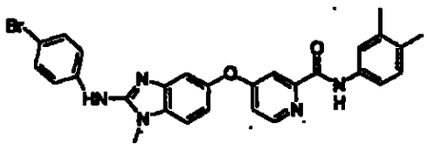
Sintetizaoa como descrito en el Ejemplo 999 usando N, *O*-dimetilhidroxilamina HCl. LCMS *m/z* 483.3 (MH^+), t_R = 2.07 min.

Ejemplo 1001



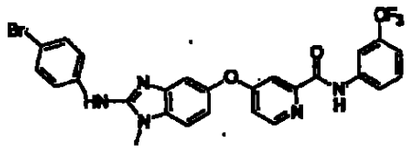
Sintetizado como descrito en el Ejemplo 999 usando 4-bromoanilina. LCMS *m/z* 594.0 (MH^+), t_R = 5.39 min.

Ejemplo 1002



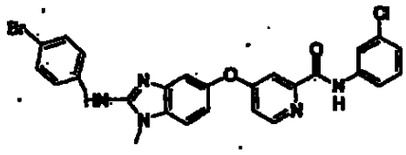
Sintetizado como descrito en el Ejemplo 999 usando 3,4-dimetilanilina. LCMS *m/z* 543.2 (MH^+), t_R = 5.39 min.

Ejemplo 1003



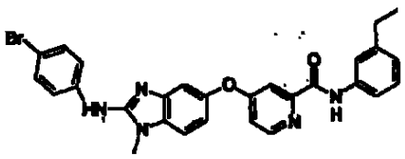
Sintetizado como descrito en el Ejemplo 999 usando3-trifluorometilanilina. LCMS *m/z* 583.1 (MH^+), t_R = 3.12 min.

Ejemplo 1004



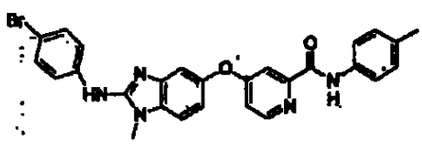
Sintetizado como descrito en el Ejemplo 999 usando3-cloroanilina. LCMS *m/z* 550.1 (MH^+), t_R = 5.28 min.

Ejemplo 1005



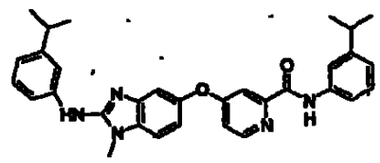
Sintetizado como descrito en el Ejemplo 999 usando3-etilanilina. LCMS *m/z* 543.2 (MH^+), t_R = 3.16 min.

Ejemplo 1006



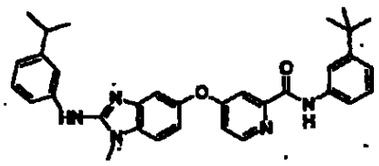
Sintetizado como descrito en el Ejemplo 1067 usando 4-metilanilina. LCMS *m/z* 529.2 (MH^+), t_R = 5.15 min.

Ejemplo 1007



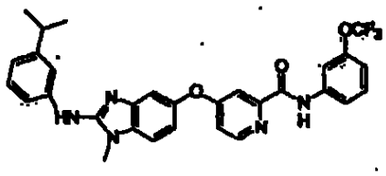
Sintetizado como descrito en el Ejemplo 999 usando 3-isopropilanilina. LCMS *m/z* 520.3 (MH^+), t_R = 5.98 min.

Ejemplo 1008



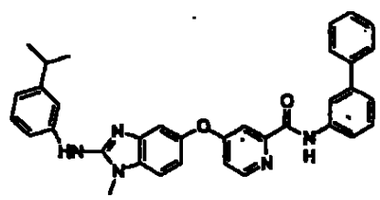
Sintetizado como descrito en el Ejemplo 999 usando 3-tert-butilanilina. LCMS *m/z* 534.3 (MH^+), t_R = 3.32 min.

Ejemplo 1009



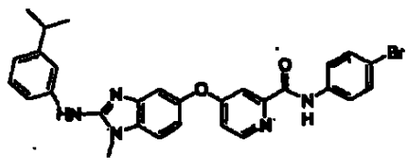
Sintetizado como descrito en el Ejemplo 999 usando 3-trifluorometoxianilina. LCMS *m/z* 562.2 (MH^+), t_R = 3.15 min.

Ejemplo 1010



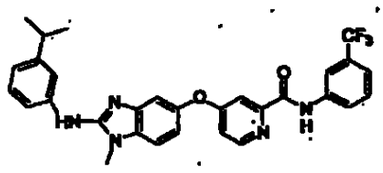
Sintetizado como descrito en el Ejemplo 999 usando 3-bifenilamina. LCMS *m/z* 554.3 (MH^+), t_R = 3.28 min.

Ejemplo 1011



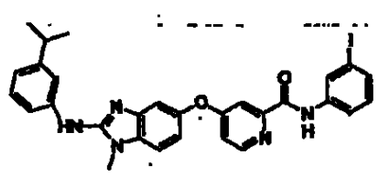
Sintetizado como descrito en el Ejemplo 999 usando 4-bromoanilina. LCMS *m/z* 557.2 (MH^+), t_R = 5.65 min.

Ejemplo 1012



Sintetizado como descrito en el Ejemplo 999 usando 3-trifluorometilanilina. LCMS *m/z* 546.3 (MH^+), t_R = 5.74 min.

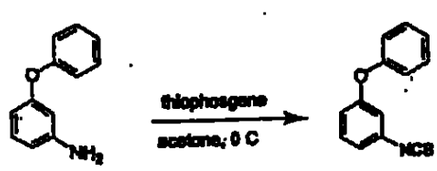
Ejemplo 1013



Sintetizado como descrito en el Ejemplo 999 usando 3-iodoanilina. LCMS *m/z* 604.2 (MH^+), t_R = 5.81 min.

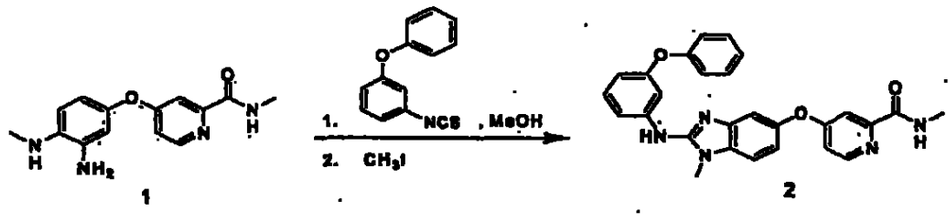
Ejemplo 1014: 4-[1-Metil-2-(3-fenoxi-fenilamino)-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico metilamina

Paso 1. Síntesis de 3-fenoxifenilisotiocianato



A una solución agitada de 3-fenoxianilina (185 mg, 1.0 mmol) en acetona (4.0 mL) a 0° C se le añadió tiofosgeno (0.23 mL, 3.0 mmol) y la reacción resultante fue mantenida por 30 minutos. La reacción fue determinada completamente por TLC (4:1 hexano/EtOAc). La reacción fue concentrada, formado el azeótropo con tolueno y tomada sin purificación adicional.

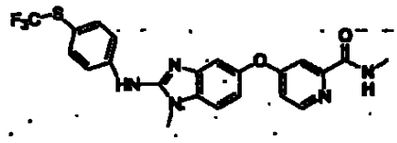
Paso 2. Síntesis de 4-[1-Metil-2-(3-fenoxi-fenilamino)-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico metilamida.



1 2

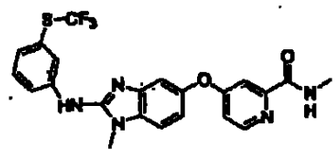
Una ampolleta de un dracma fue cargada con una solución de 3-fenoxifenilisotiocianato (23 mg, 0.1 mmol), diamina 1 (27 mg, 0.1 mmol) y MeOH (0.5 mL) y la reacción fue sacudida durante la noche. La reacción fue concentrada y el residuo resultante fue purificado en HPLC fase-reversible. LCMS *m/z* 466.3 (MH^+), t_R = 2.40 min.

Ejemplo 1015



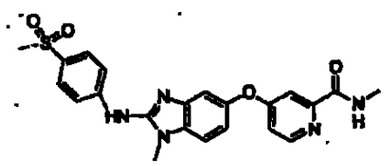
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 4-trifluorometiltiofenilisotiocianato. LCMS *m/z* 474.5 (MH^+), t_R = 3.76 min.

Ejemplo 1016



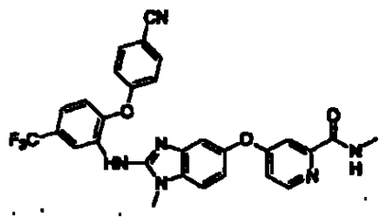
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 3-trifluorometiltiofenilisotiocianato. LCMS *m/z* 474.5 (MH^+), t_R = 3.65 min.

Ejemplo 1017



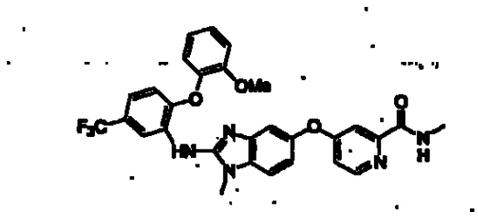
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 4-1-isotiocianato-4-metanosulfonil benceno, preparado como en el Paso 1. LCMS *m/z* 452.5 (MH^+), t_R = 2.86 min.

Ejemplo 1018



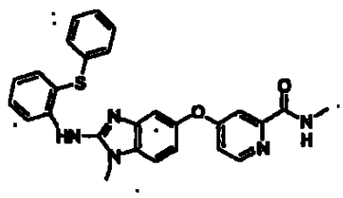
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 4-(2-isotiosonato-4-trifluorometil-fenoxi)-benzonitrilo, preparado como en el Paso 1. LCMS *m/z* 559.6 (MH^+), t_R = 4.22 min.

Ejemplo 1019



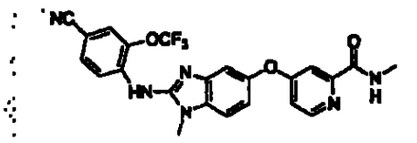
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2-(2-metoxi-fenoxi)-5-trifluorometil-fenilisotiocianato, preparado como en el Paso 1. LCMS *m/z* 564.6 (MH^+), t_R = 4.42 min.

Ejemplo 1020



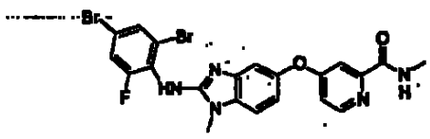
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2-fenilsulfanil-fenilisotiocianate, preparado como en el Paso 1. LCMS *m/z* 482.5 (MH^+), t_R = 3.85 min.

Ejemplo 1021



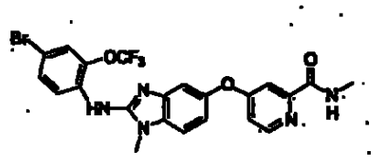
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 4-isotiocianato-3-trifluorometoxi-benzonitrilo, preparado como en el Paso 1. LCMS *m/z* 483.4 (MH^+), t_R = 2.35 min.

Ejemplo 1022



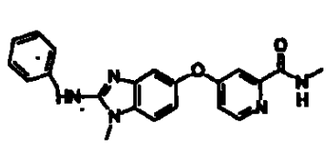
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2,4- dibromo-6-fluorofenilisotiocianato. LCMS *m/z* 550.3 (MH^+), t_R = 3.50 min.

Ejemplo 1023



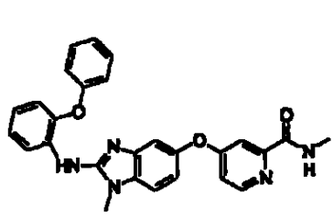
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 4-bromo-2-trifluorometoxi-fenilisotiocianato. LCMS *m/z* 537.3 (MH^+), t_R = 3.89 min.

Ejemplo 1024



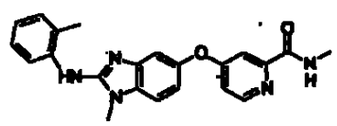
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando fenilisotiocianato. LCMS *m/z* 374.5 (MH^+), t_R = 2.84 min.

Ejemplo 1025



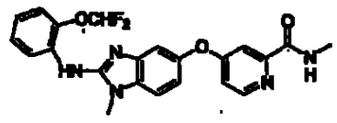
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2-fenoxi-fenilisotiocianato, preparado como en el Paso 1. LCMS *m/z* 466.5 (MH^+), t_R = 2.37 min.

Ejemplo 1026



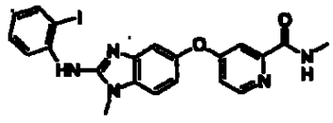
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2-metil-fenilisotiocianato. LCMS *m/z* 388.5 (MH^+), t_R = 2.99 min.

Ejemplo 1027



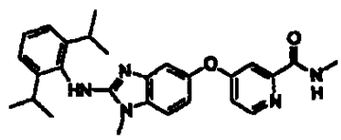
Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2-difluorometoxi-fenilisotiocianato. LCMS *m/z* 440.5 (MH^+), t_R = 3.13 min.

Ejemplo 1028



Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2-iodo-fenilisotiocianato. LCMS *m/z* 500.4 (MH^+), t_R = 2.07 min.

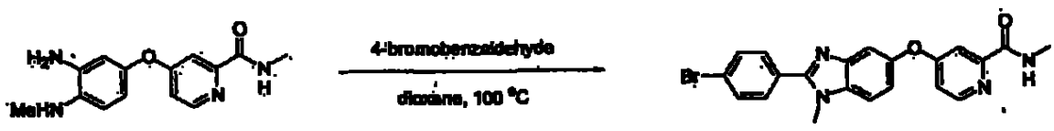
Ejemplo 1029



Sintetizado como descrito en el Ejemplo 1014 Paso 2 usando 2,6-diisopropil-fenilisotiocianato. LCMS *m/z* 430.5 (MH^+), t_R = 2.27 min.

Ejemplo 1030

4-[2-(4-Bromofenil)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácidocarboxílico metilamida.

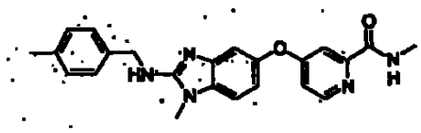


1 2

Una mezcla de diamina 1 (137 mg, 0.36 mmol) y 4-bromobenzaldehido (66 mg, 0.50 mmol) en dioxano seco (2 mL) fue calentada a 100° C por 16 horas. La mezcla de la reacción fue dejada enfriar a temperatura ambiente y luego fue concentrada. El residuo resultante fue purificado por HPLC fase-reversada para proveer a 2 como una sal TFA: LCMS *m/z* 437.1 (MH^+), t_R = 2.16 min.

Ejemplo 1031

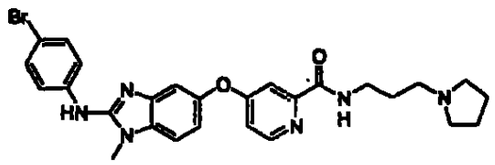
4-[1-Metil-2-(4-metilbencilamino)-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico metilamida.



Preparado como Ejemplo 120b usando 4-metilbencil tioisocianato: LCMS *m/z* 402.2 (MH^+), t_R = 1.91 min.

Ejemplo 1032

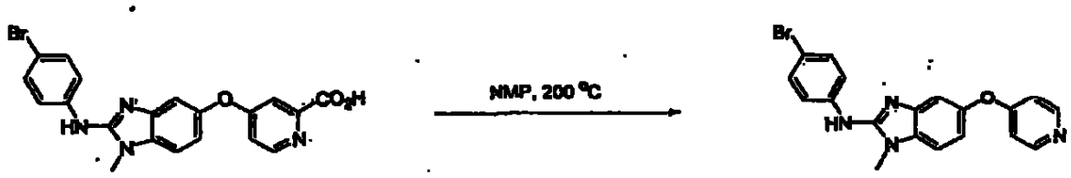
4-[2-(4-Bromofenilamino)-1-metil-1H-bencimidazol-5-iloxi]-piridin-2-ácido carboxílico (3-pirrodilin-1-il-propil)-amida.



Preparado como el Ejemplo 371 usando amida-1-(3-aminopropil)pirrolidin: LCMS *m/z* 549.5 (MH^+), t_R = 2.97 min.

Ejemplo 1033

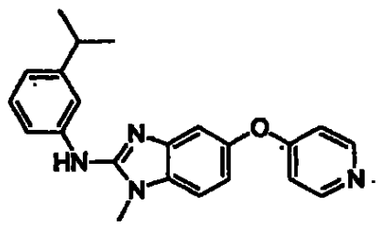
(4-Bromofenil)-[1-metil-5-(piridin-4-iloxi)-1H-benzoimidazol-2-il]-amina.



1 2

Una solución de ácido 1 (44 mg, 0.1 mmol) en NMP seco (1 mL) fue calentada a 200° C por 20 minutos. La reacción fue dejada a enfriar a temperatura ambiente y la mezcla de la reacción cruda fue directamente purificada en HPLC fase-revertida para obtener 2 como sal TFA: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J*= 7.4 Hz, 2 H), 7.70 (d, *J*= 8.5 Hz, 1 H), 7.68 (d, *J*= 8.8 Hz, 2 H), 7.45 (d, *J*= 8.8 Hz, 2 H), 7.42 (d, *J*= 7.4 Hz, 2 H), 7.32 (d, *J*= 2.2 Hz, 1 H), 7.26 (dd, *J*= 2.2 Hz, 1 H), 3.86 (s, 3 H); LCMS *m/z* 395.0 (MH^+), t_R = 1.48 min.

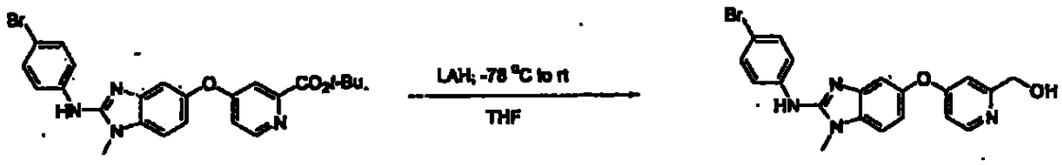
Ejemplo 1034



LCMS *m/z* 359.3 (MH^+), t_R = 1.91 min.

Ejemplo 1035

{4-[2-(4-Bromofenilamino)-1-metil-1H-bencimidazol-5-iloxi]-piridin-2-il}-metanol



1 2

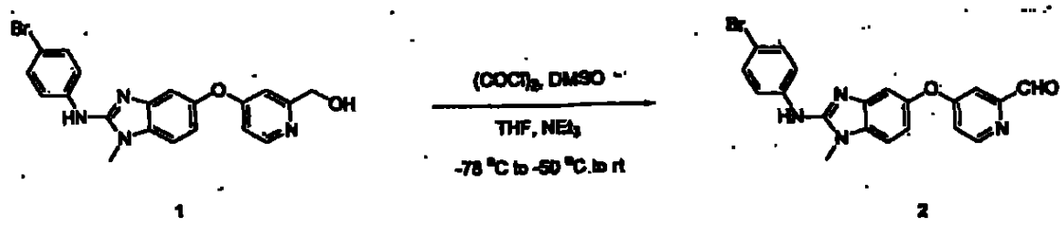
Una suspensión de *t*-butil ester 1 (496 mg, 1.0 mmol) en THF seco (3 mL) fue añadido a una suspensión agitada de LAH (61 mg, 1.6 mmol) en THF seco (2 mL) a -78° C. La reacción fue dejada a calentar a temperatura ambiente por 3 horas. Luego de que la reacción fue estimada como terminada por LCMS, agua (30 ul, 1.7 mmol) y NaF (270 mg, 6.4 mmol) fueron añadidos y la mezcla resultante fue agitada vigorosamente durante la noche a temperatura ambiente. La mezcla cruda fue filtrada por medio de Celite y los sólidos restantes fueron enjuagados con EtOAc. Las porciones orgánicas combinadas fueron concentradas y una porción del residuo resultante fue purificado por HPLC fase-reversible para producir alcohol 2 como una sal TFA: ^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (d, *J*= 7.2 Hz, 1 H), 7.72 (d, *J*= 8.5 Hz, 1 H), 7.69 (d, *J*= 8.8 Hz, 2 H), 7.45 (d, *J*= 8.8 Hz, 2 H), (m, 3 H) 7.28 (d, *J*= 2.2, 8.5 Hz, 1 H), 4.86 (app s, 2 H), 3.87 (s, 3 H); LCMS *m/z* 425.1 (MH^+), t_R = 1.49 min.

Ejemplo 1036

(4-Bromofenil)-[1-metil-5-(2-metilaminometil-piridil-4-iloxi)-1H-benzoimidazol-2-il]-amina

Preparación general para Bencil Aminas

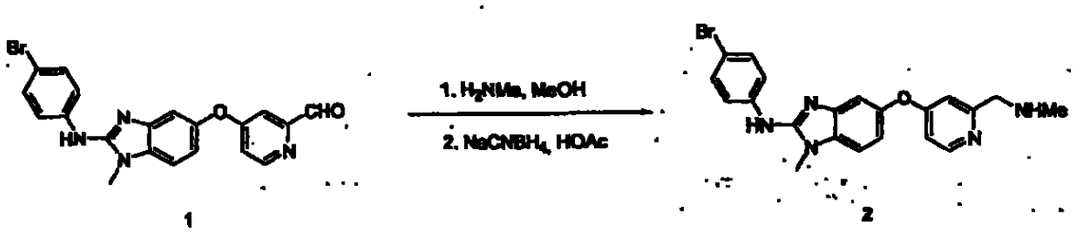
Paso 1. 4-[2-(4-Bromofenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-carboxaldehida



1 2

DMSO seco (0.1 mL, 1.4 mmol) fue añadido a una solución de oxalil cloruro (0.11 mL, 1.3 mmol) en THF seco (2 mL) a -78° C y la solución resultante fue mantenida a -78° C por 30 minutos. Una solución alcohol 1 en THF seco (2 mL) fue luego introducida y la reacción resultante fue mantenida a -78° C por 30 minutos, luego a -50° C por 45 minutos. Trietilamina (0.5 mL, 3.6 mmol) fue añadida y la reacción fue dejada calentar a temperatura ambiente por mas de una hora. La reacción fue apagada con agua, y separada con EtOAc. Las capas fueron separadas y la porción acuosa fue extractada con EtOAc (3 X). Las fases orgánicas combinadas fueron lavadas con salmuera, secadas ($MgSO_4$), y concentradas. El residuo resultante es llevado sin purificación adicional.

Paso 2. (4-Bromofenil)-[1-metil-5-(2-metilaminometil-piridin-4-iloxi)-1 H-benzoimidazol-2-il]-amina.

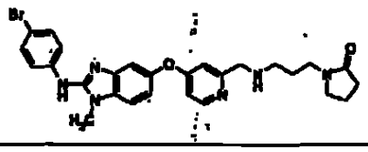


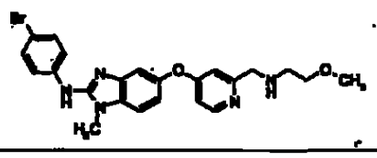
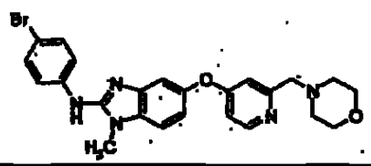
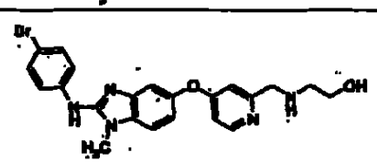
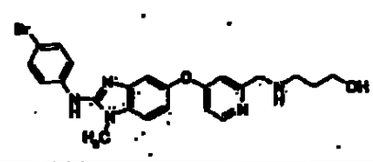
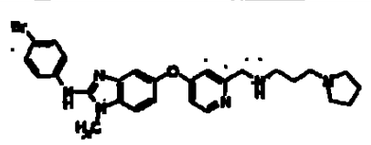
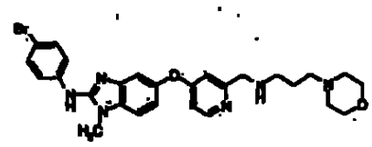
1 2

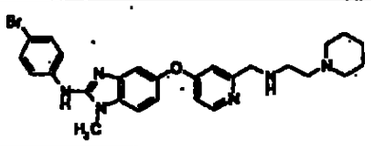
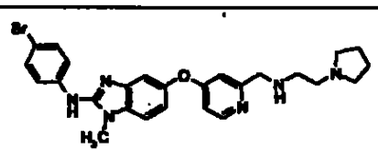
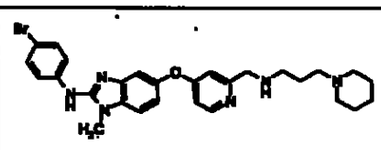
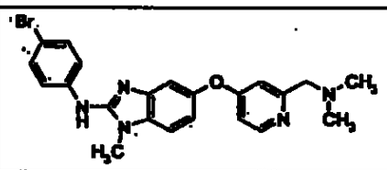
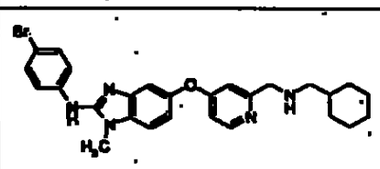
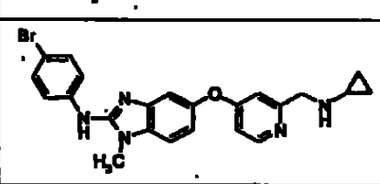
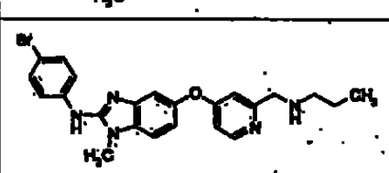
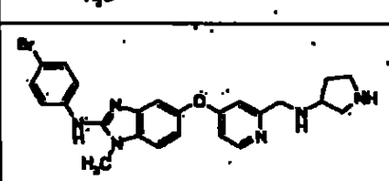
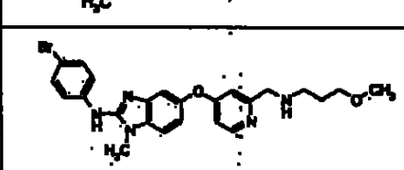
Metil amina (0.3 mL, 0.6 mmol, 2.0 M en MeOH) fue añadida a una solución de aldehido 1 en MeOH (1 mL) y la reacción fue mantenida a temperatura ambiente por 2 días. La reacción fue acidificada por la adición de ácido acético (pH = 3-4), y un exceso de $NaBH_3CN$ fue añadido. La reacción fue mantenida por 2 días y luego concentrada. La mezcla de la reacción cruda fue disuelta en EtOAc y separada con una solución $NaHCO_3$ acuosa saturada. Las capas fueron separadas y la fase acuosa fue extractada con EtOAc (3 X). Las porciones orgánicas combinadas fueron lavadas con agua salada, secadas ($MgSO_4$), y concentradas. El residuo resultante fue purificado con HPLC fase-reversible para obtener *N*-metil amina **2** como una sal TFA: ^{1}H NMR (300 MHz, CD_3OD) δ 8.48 (d, *J*= 5.8 Hz, 1 H), 7.72 (d, *J*= 8.8 Hz, 2 H), 7.67 (d, *J*= 9.4 Hz, 1 H), 7.43 (d, *J*= 8.8 Hz, 2 H), 7.20 (dd, *J*= 2.2, 9.4 Hz, 1 H), 7.19 (d, *J*= 2.2 Hz, 1 H), 7.02 (d, *J*= 2.2 Hz, 1 H), 6.90 (dd, *J*= 2.2, 5.8 Hz, 1 H), 4.27 (s, 2 H) 3.86 (s, 3 H) 2.76 (s, 3 H); LCMS *m/z* 438.5 (MH^+), t_R = 1.85 min.

Las siguientes bencilaminas tabuladas fueron preparadas por el método descrito anteriormente como en el ejemplo 1036 usando la amina apropiadas.

Tabla 14

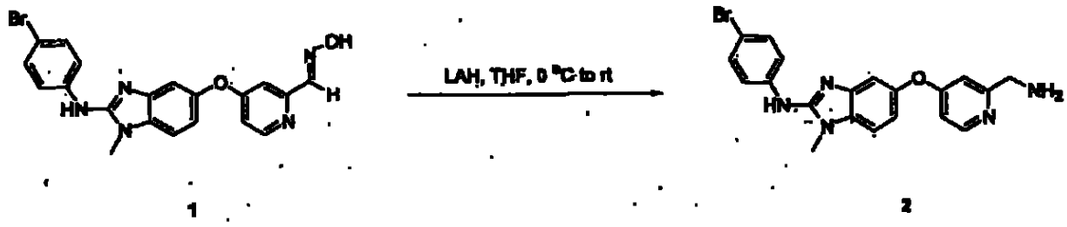
Ejemplo	Estructura	LCMS (MH^+) *m/z*	TIEMPO t_R (min)
		549.1	1.62

Ejemplo	Estructura	LCMS (MH^+) *m/z*	TIEMPO t_R (min)
		482.2	1.94
		494.1	1.59
		468.2	1.87
		483.3	1.83
		536.2	1.87
		552.2	1.84

Ejemplo	Estructura	LCMS (MH^+) *m/z*	TIEMPO t_R (min)
		536.4	1.80
		522.3	1.76
		550.4	1.80
		452.3	2.70*
		521.4	3.63*
		465.3	2.75*
		467.3	2.86*
		494.2	1.82
		497.2	2.40

Ejemplo 1053

[5-(2-Aminoetil-piridin-4-iloxi)-1-metil-1H-benzoimidazol-2-il]-(4-bromofenil)-amina.

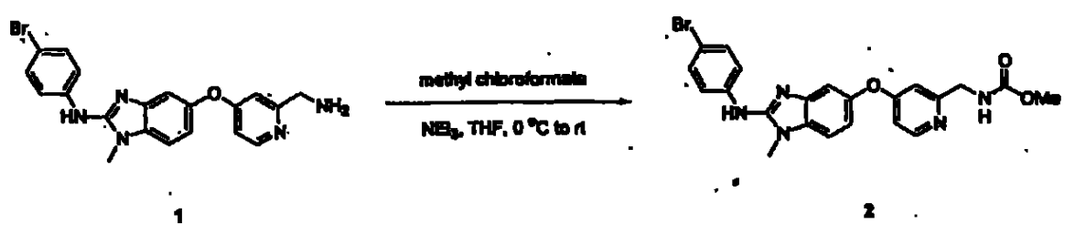


1 2

LAH (98 mg, 2.5 mmol) fue añadido por porciones a una solución agitada de oxima 1 (225 mg, 0.5 mmol) en THF seco (3 mL) a 0° C. Luego de la adición, el baño frío fue removido y la reacción fue dejada calentar a temperatura ambiente durante la noche. La reacción fue apagada con adición de agua (0.1 mL), 10% w/w de solución NaOH acuosa (0.1 mL), y agua (0.3 mL). El producto resultante fue agitado a temperatura ambiente por una hora y filtrado por medio de Celite. Los sólidos resultantes fueron enjuagados con EtOAc y las porciones orgánicas fueron combinadas y concentradas. El residuo crudo fue purificado por HPLC fase-reversible para obtener bencil amina 2 como sal TFA: LCMS *m/z* 424.1 (MH^+), t_R = 1.87 min.

Ejemplo 1054

{4-[2-(4-Bromofenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-il-metil}-ácido carbámico metil ester.

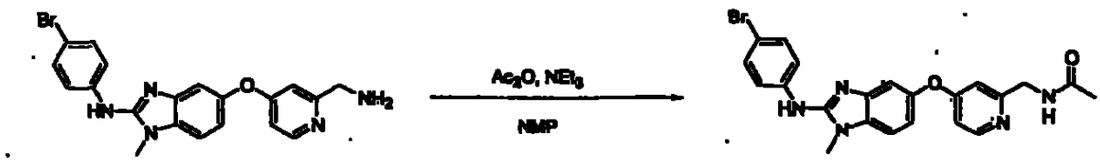


1 2

Metil cloroformato (6μL, 0.08 mmol) fue añadido a una solución de bencilamina 1 (21 mg, 0.05 mmol) y trietilamina (69μL, 0.5 mmol) en THF seco (1 mL) a 0° C. La reacción fue mantenida a 0° C por 20 minutos, y luego a temperatura ambiente por 2 horas. La mezcla de la reacción fue concentrada y purificada por HPLC en fase-reversible para obtener metil carbamato 2 como una sal TFA: LCMS *m/z* 482.2 (MH^+), t_R = 1.96 min.

Ejemplo 1055

N-{4-[2-(Brominifelamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ilmetil}acetamida



1 2

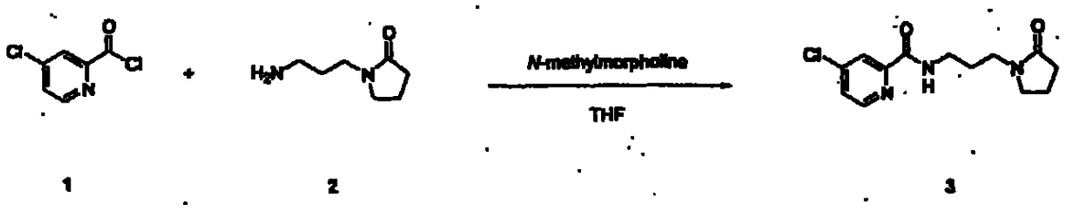
A una solución de bencil amina 1 (17 mg, 0.04 mmol) en NMP seco (2 mL) fue añadido trietilamina 0.06 mL, 0.4 mmol) y anhídrido acetico (0.04 mL, 0.4 mmol). La reacción resultante fue mantenida a temperatura ambiente durante la noche y purificada directamente por HPLC fase-reversible para obtener acetamida 2 como una sal TFA: LCMS *m/z* 466.3 (MH^+), t_R = 1.78 min.

Ejemplo 1056

4-[2-(3-etilfenilamino-1-metil-1H-benzoimidazol-5-iloxi)-piridin-2-ácido carboxílico [3-(2-oxo-pirrolidin-il)-propil]-amida

Preparación general para N-(3-Aminopropil)-pirrolidinona Amidas

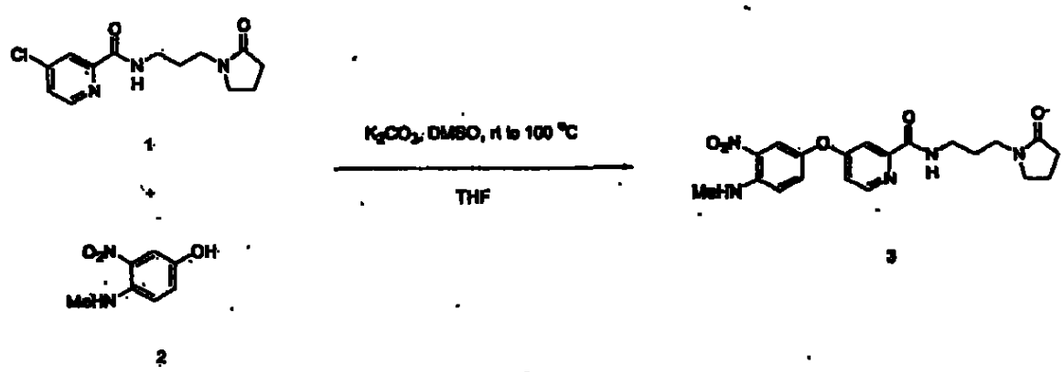
Paso1: 4-Cloro-piridin-2-ácido carboxílico[3-(2-oxo-pirrolidin-1-il)-propil]-amida



1 2 3

Ácido clorhiírico 1 (2.12 g, 10 mmol) fue tratado con N-metilmorfilina (4.5 mL, 41 mmol) y N-(3-aminopropil)-pirrolidinona 2 (1.6 m, 11 mmol) en THF seco (40 mL). La reacción fue mantenida durante la noche y concentrada. El residuo fue disuelto en EtOAc y separado con agua. La porción acuosa fue extraída con EtOAc (3 X) y las fases orgánicas combinadas fueron lavadas con agua salada, secadas ($MgSO_4$), y concentradas. El residuo crudo fue purificado por destilación Kugelrohr (0.5 mmHG, 170-200° C para dar 3.

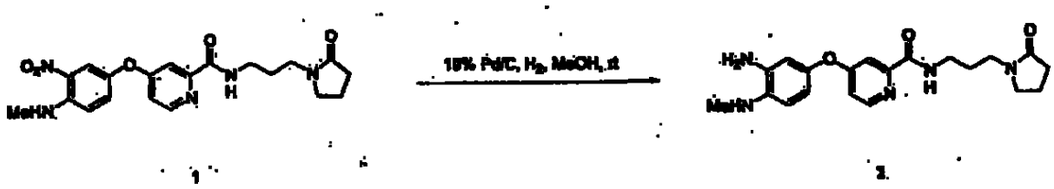
Paso 2. 4-(4-Metilamino-3-nitrofenoxi)-piridin-2-ácido carboxílico [3-(2-oxo-pirrodilil-il)-propil]-amida.



1 2 3

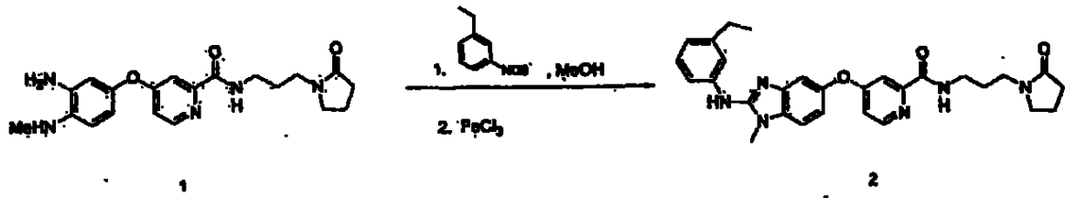
Preparada como Ejemplo 120b con las sustituciones apropiadas. Amida 3 puede ser purificada por cromatogRafía flash (95:5 CH2Cl2/MMeOH). También puede ser purificado aún más con recristalización de MeCN.

Paso 3. 4-(3-Amino-4-metilamino-fenoxi)-piridil-2-ácido carboxílico [3-(2-oxo-pirrolidin-il)-propil]-amida



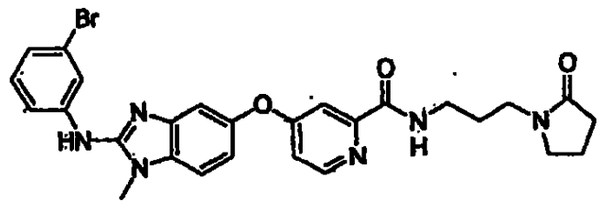
Preparada como Ejemplo 120b.

Paso 4. 4-[2-(3-Etilfenilamino)-1-metil-1H-benzoimidazol-5-iloxi]-piridin-2-ácido carboxílico [3-(-oxo-pirrolidin-il)-propil]-amida



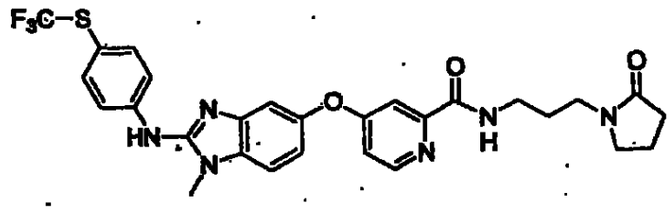
Preparado como el Ejemplo 120b para obtener bencimidazol **2** como una sal TFA: LCMS *m/z* 513.3 (MH^+), t_R = 2.22 min.

Ejemplo 1057



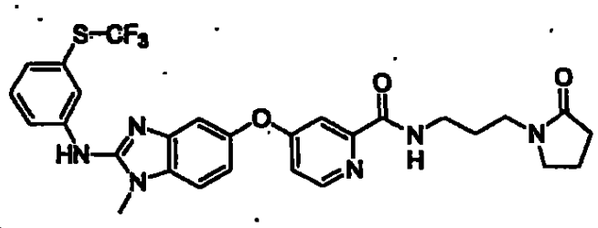
Preparada como el Ejemplo 1056: LCMS *m/z* 563.2 (MH^+), t_R = 2.15 min.

Ejemplo 1058



Preparada como el Ejemplo 1056: LCMS *m/z* 585.3 (MH^+), t_R = 2.55 min.

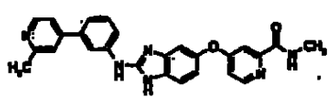
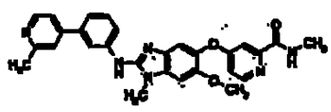
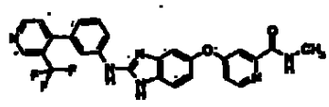
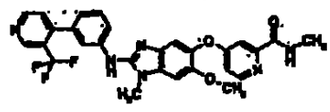
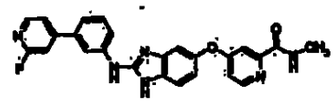
Ejemplo 1059

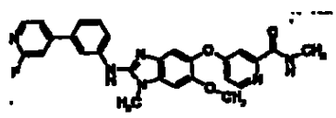
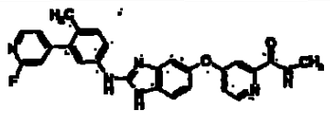
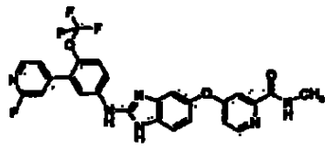
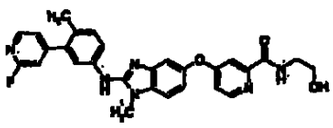
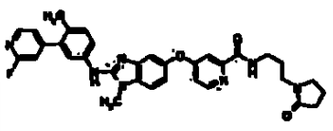
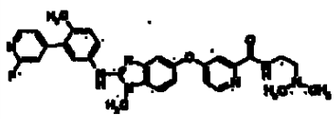
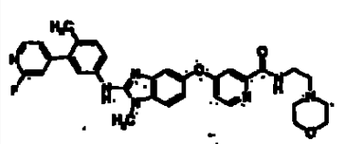
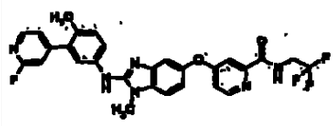


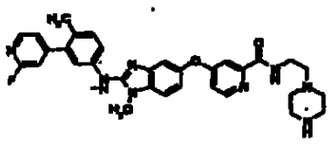
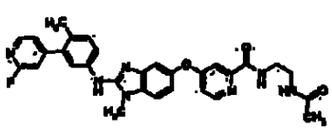
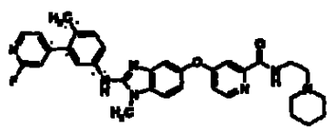
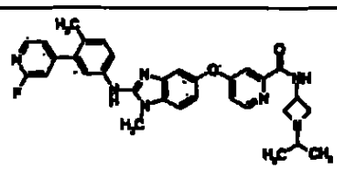
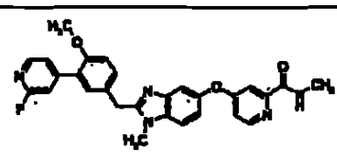
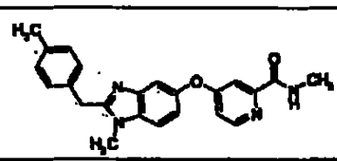
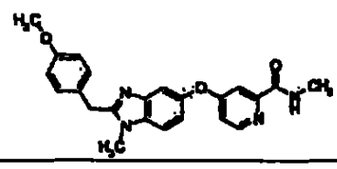
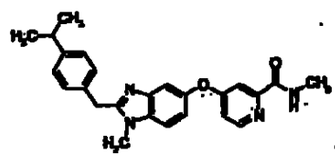
Preparada como el Ejemplo 1056: LCMS *m/z* 563.2 (MH^+), t_R = 2.50 min.

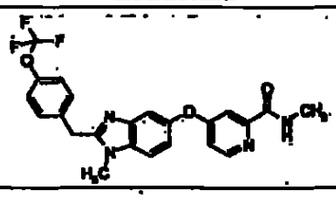
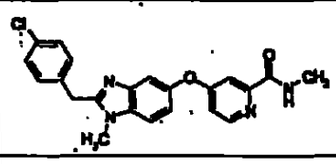
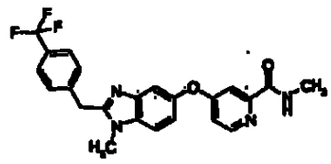
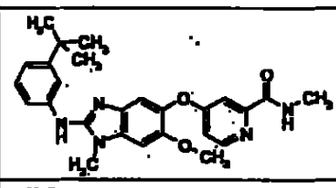
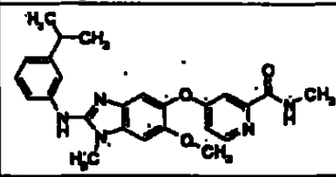
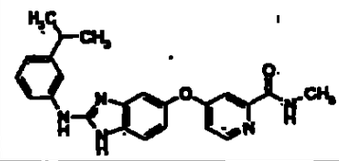
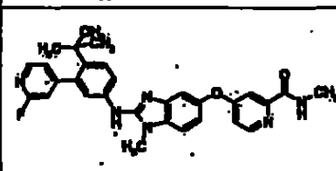
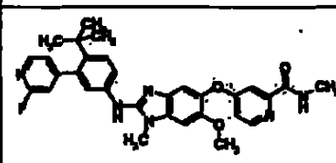
Los siguientes compuestos adicionales fueron preparados siguiendo los procedimientos de los Ejemplos indicados:

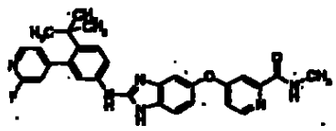
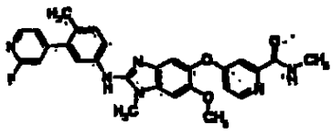
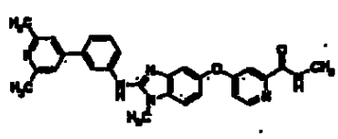
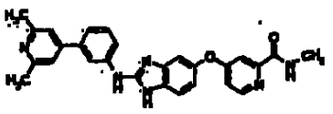
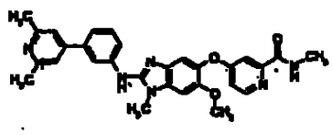
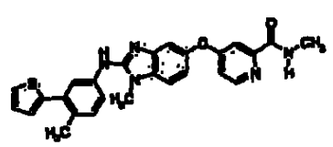
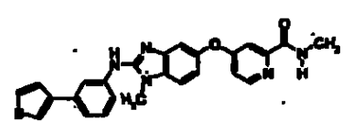
Tabla 15

Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
1060		N-metil-4-[(2-{[3-(2-metil-piridin-4-il)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	451.5	702
1061		N-metil-4-[(1-metil-6-(metiloxi)-2-{[3-(2-metil-piridin-4-il)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2carboxamida	495.6	702
1062		N-metil-4-{[2-({3-[3-(trifluorometil)piridin-4-il]-fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	505.5	702
1063		N-metil-4-{[1-metil-6-(metiloxi)-2-({3-[3-(trifluorometil)piridin-4-il]-fenil}amino)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	549.5	702
1064		4-[(2-{[3-(2-fluoropiridin-4-il)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metil-piridin-2-carboxamida	455.5	702

Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
1065		4-{[2-{[3-(2-fluoropiridin-4-il)fenil]amino}-1-metil-6-(metiloxi)1H-bencimidazol-5-il]oxi}-N-metil-piridin-2-carboxamida	499.5	702
1066		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	469.5	702
1067		4-{[2-({3-(2-fluoropiridin-4-il)-4[(trifluorometil)oxi]fenil}amino)-1H-bencimidazol-5-il]oxi}-N-metil-piridin-2-carboxamida	539.5	702
1068		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-hidroxietil)-piridin-2-carboxamida	513.5	483
1069		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[3-(2-oxopirrolidin-1-il)propil]piridin-2-carboxamida	594.7	483
1070		N-[2-(dimetilamino)etil]-4-[(2-{[3-(2-fluoropiridin-4-il)-4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	540.6	483
1071		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-morfolin-4-iletil)-piridin-2-carboxamida	582.6	483
1072		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2,2,2-trifluoroetil)-piridin-2-carboxamida	551.5	483

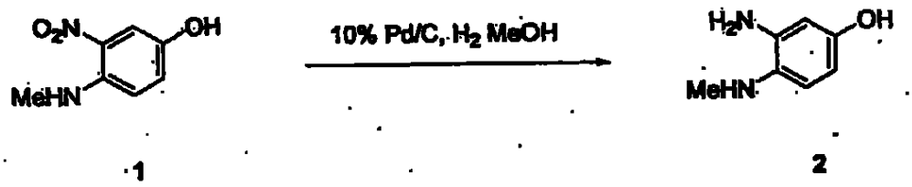
Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
1073		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperazin-1-iletil)-piridin-2-carboxamida	581.7	483
1074		N-[2-(acetilamino)etil]-4-[(2-{[3-(2-fluoropiridin-4-il)-4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	554.6	483
1075		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-(2-piperidin-1-iletil)-piridin-2-carboxamida	580.7	483
1076		4-[(2-{[3-(2-fluoropiridin-4-il)4-metilfenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-[1-(1-metiletil)-acetidin-3-il]piridin-2-carboxamida	566.7	636
1077		4-[(2-{[3-(2-fluoropiridin-4-il)4-(metiloxi)fenil]metil}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	498.5	636
1078		N-metil-4-({1-metil-2-[(4-metilfenil)metil]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	387.5	636
1079		N-metil-4-[(1-metil-2-{[4-(metiloxi)fenil]metil}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	403.5	636
1080		N-metil-4-[(1-metil-2-{[4-(1-metiletil)fenil]metil}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	415.5	636

Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
1081		N-metil-4-{[1-metil-2-({4-[(trifluorometil)oxi]fenil}metil)-1H-bencimidazol-5-il]oxi}-piridin-2-carboxamida	457.4	636
1082		4-({2-[(4-clorofenil)metil]-1-metil-1H-bencimidazol-5-il}oxi)-N-metilpiridin-2-carboxamida	407.9	636
1083		N-metil-4-[(1-metil-2-{[4-(trifluorometil)fenil]metil}-1H-bencimidazol-5-il)oxi]-piridin-2-carboxamida	441.4	636
1084		4-{[2-{[3-(1,1-dimetiletil)-fenil]amino}-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	460.5	703
1085		N-metil-4-{[1-metil-2-{[3-(1-metiletil)fenil]amino}-6-(metiloxi)-1H-bencimidazol-5-il]oxi}piridin-2-carboxamida	446.5	703
1086		N-metil-4-[(2-{[3-(1-metil-etil)fenil]amino}-1H-bencimidazol-5-il)oxi]piridin-2-carboxamida	402.5	1
1087		4-[(2-{[4-(1,1-dimetiletil)-3-(2-fluoropiridin-4-il)fenil]-amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metil-piridin-2-carboxamida	525.6	702
1088		4-{[2-{[4-(1,1-dimetiletil)-3-(2-fluoropiridin-4-il)fenil]amino}-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamida	555.6	702

Ejemplo	Estructura	Nombre	MH+	Sintetizado como en el ejemplo
1089		4-[(2-{[4-(1,1-dimetiletil)-3-(2-fluoropiridin-4-il)fenil]-amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	511.6	702
1090		4-{[2-{[3-(2-fluoropiridin-4-il)-4-metilfenil]amino}-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2carboxamida	513.5	702
1091		4-[(2-{[3-(2,6-dimetilpiridin-4-il)fenil]amino}-1-metil-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamida	479.6	702
1092		4-[(2-{[3-(2,6-dimetilpiridin-4-il)fenil]amino}-1H-bencimidazol-5-il)oxi]-N-metilpiridin-2-carboxamina	465.5	702
1093		4-{[2-{[3-(2,6-dimetilpiridin-4-il)fenil]amino}-1-metil-6-(metiloxi)-1H-bencimidazol-5-il]oxi}-N-metilpiridin-2-carboxamina	509.6	702
1094a		N-metil-4-({1-metil-2-[(4-metil-3-tien-2-ilfenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	470.6	702
1094b		N-metil-4-({1-metil-2-[(3-tien-3-ilfenil)amino]-1H-bencimidazol-5-il}oxi)-piridin-2-carboxamida	556.5	702

Preparación general para Fenólicos Bencimidazoles

3-Amino-4-Metilaminofenol

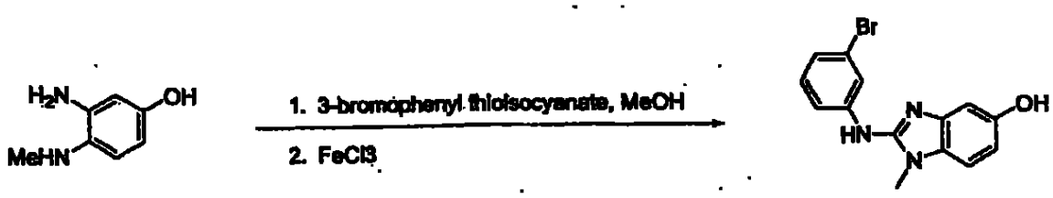


1 2

Diamina 2 es preparada como Ejemplo 120b de nitroanilina 1.

Ejemplo 1095

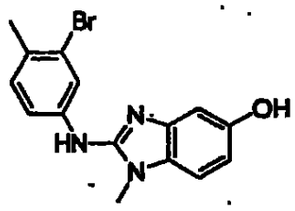
2-(3-Bromofenilamino)-1-metil-1H-benzoimidazol-5-ol



1 2

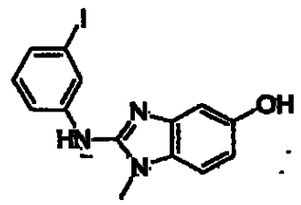
Bencimidazol 2 fue preparado como el Ejemplo 120b: LCMS *m/z* 318.1 (MH^+), t_R = 2.07 min.

Ejemplo 1096



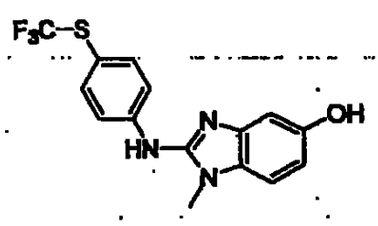
LCMS *m/z* 332.1 (MH^+), t_R = 2.22 min.

Ejemplo 1097



LCMS *m/z* 366.1 (MH^+), t_R = 2.13 min.

Ejemplo 1098

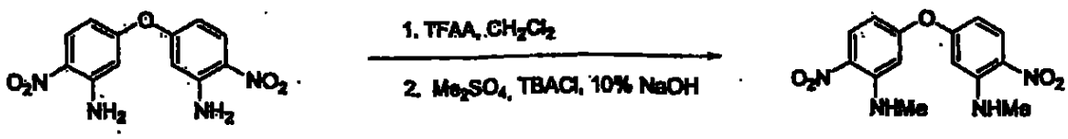


LCMS *m/z* 340.2 (MH^+), t_R = 2.39 min.

Ejemplo 1099

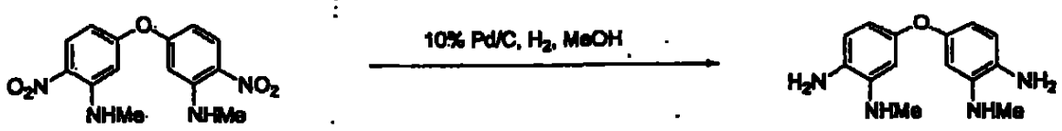
Preparación de bis-Bencimidazoles simétricos

Paso 1. 4,4'-dimetilamino-3,3'-dinitro difenil eter



Difenil eter **2** fue preparado usando el método descrito en Ejemplo 120b: ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (br s, 2 H) 7.75 (d, *J*= 3.0 Hz, 2 H), 7.29 (app d, *J*= 3.0 Hz, 1 H), 6.87 (d, *J*= 9.5 Hz, 2 H), 3.05 (d, *J*= 5.2 Hz, 6 H).

Paso 2. 4,4'-Dimetilamino-3,3'-diamino difenil eter

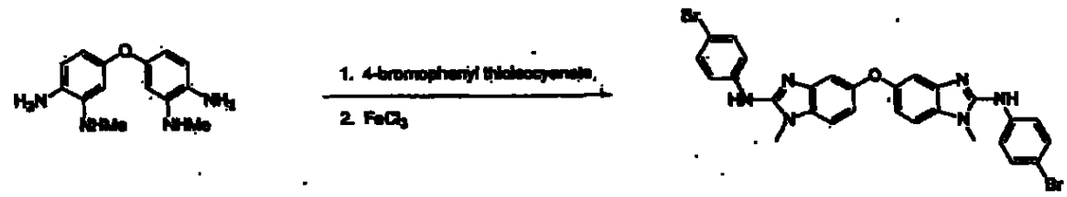


1 2

Tetramina **2** fue preparada usando el método descrito en Ejemplo 120b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, *J*= 8.5 Hz, 2 H), 6.47 (app d, *J*= 2.8, 8.5 Hz, 2 H), 6.41 (d, *J*= 2.8 Hz, 2 H), 3.40 (br s, 4 H), 3.06 (br s, 2 H) 2.84 (d, *J*= 5.2 Hz, 6 H).

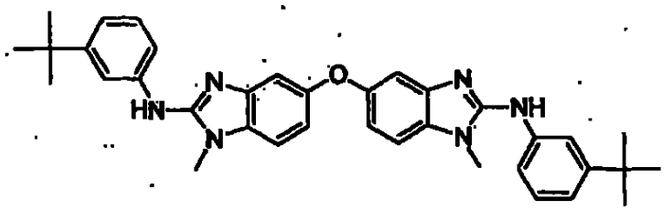
Ejemplo 1100

bis-5-[2-(3-Bromofenilamino)-1-metil-1H-benzoimidazol]-eter



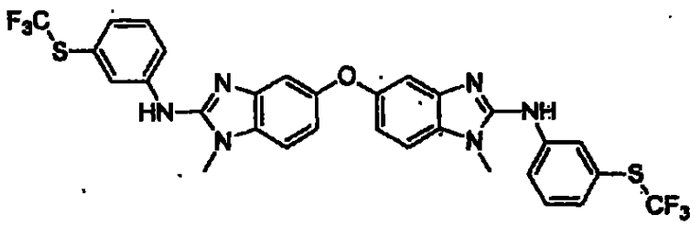
Preparado como el Ejemplo 120b: LCMS *m/z* 617.1 (MH^+), t_R = 2.27 min.

Ejemplo 1101



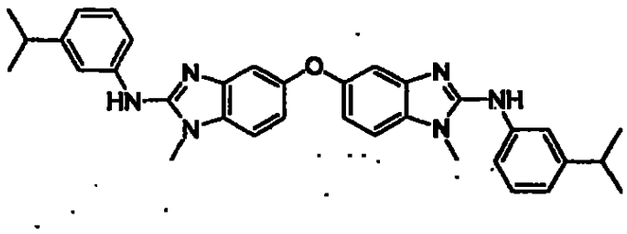
Preparado como el Ejemplo 120b: LCMS *m/z* 573.4 (MH^+), t_R = 2.78 min.

Ejemplo 1102



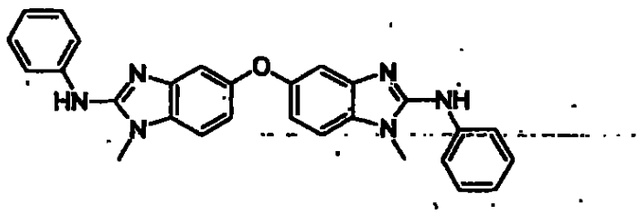
Preparado como el Ejemplo 120b: LCMS *m/z* 661.2 (MH^+), t_R = 2.83 min.

Ejemplo 1103



Preparado como el Ejemplo 120b: LCMS *m/z* 545.4 (MH^+), t_R = 2.73 min.

Ejemplo 1104

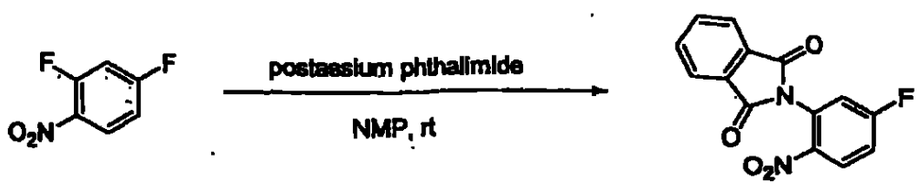


Preparado como el Ejemplo 120b: LCMS *m/z* 461.3 (MH^+), t_R = 1.98 min.

Ejemplo 1105

Preparación de Derivados Benzo

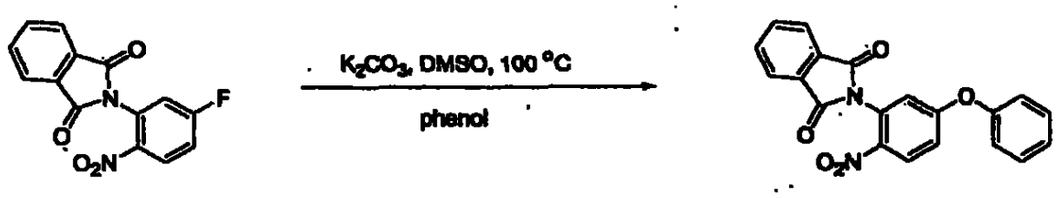
2-(N-ftalimido)-4-fluoronitrobenceno



Una suspensión de 2,4-difluoronitrobenceno (15.9g, 100 mmol) y potasio ftalimide (16.5g, 100 mmol) fue agitada en NMP seco (50 mL) por 3 días. La solución de la reacción fue vertida dentro de MTBE y el precipitado resultante fue recolectado por medio de filtración. Los sólidos fueron lavados con MTBE (3 X) y el líquido inicial fue extraído con MTBE (3 X). Las porciones de los compuestos orgánicos combinados fueron lavadas con agua (3 X) y concentradas para dar como resultado un sólido amarillo que fue combinado con el producto original del precipitado. El sólido crudo combinado fue purificado por recristalización con tolueno caliente, y los cristales fueron lavados con MTBE frio. ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.31 (dd, *J*= 5.2, 9.1 Hz, 1 H), 7.98 (m, 4H), 7.69 (dd, *J*= 2.8, 9.1 Hz, 1 H), 7.62 (ddd, *J*= 1.7, 2.8, 7.7 Hz, 1 H).

Ejemplo 1106

2.(N-Ftalimido)-4-fenoxinitrobenceno

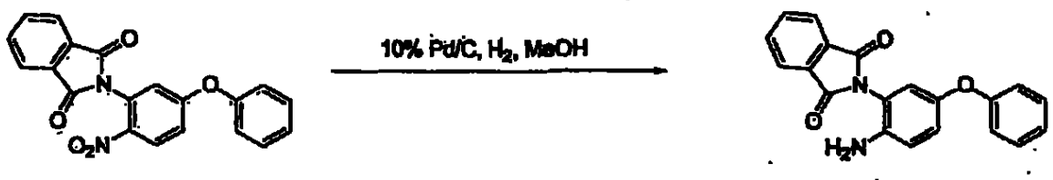


1 2

2-(N-ftalimido)-4-fenoxinitrobenceno **2** fue preparado usando un procedimiento similar al del Ejemplo 120b.

Ejemplo 1107

2-(N-ftalimido)-4-fenoxianilina

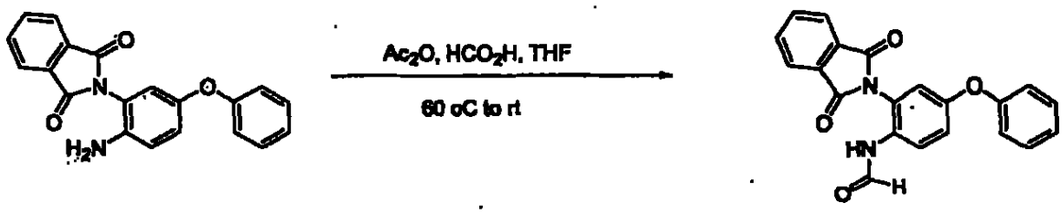


1 2

2-(N-Ftalimido)-4-fenoxianilina 2 fue obtenida por medio de la reducción de 2-(N-ftalimido)-4-fenoxinitrobenceno 1 como descrito en el Ejemplo 120b.

Ejemplo 1108

N-[2-(N-ftalimido)-4-fenoxi-fenil]-formamida

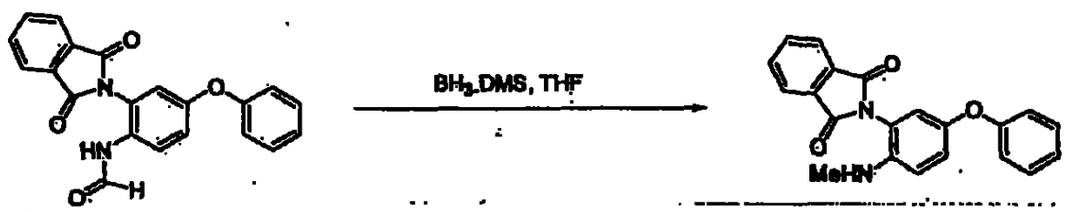


1 2

Una mezcla de ácido fórmico (.12 mL, 5.3 mmol) y anhídrido acético (0.24 mL, 2.5 mmol) fue calentado a 60° C por 2 horas. Luego de dejar lo enfriar a temperatura ambiente, la solución de anilina 1 387 mg, 1.0 mmol) en THF seco (1 mL) fue añadida y la reacción fue mantenida durante la noche. La reacción fue concentrada y el resultante residuo crudo fue directamente usado en el siguiente paso.

Ejemplo 1109

N-Metil-[2-(N-ftalimido)-4-fenoxi]-anilina

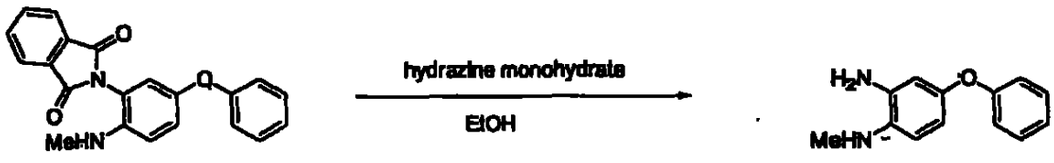


1 2

Una solución de formamida 1 fue tratada con una solución BH_3-DMS (2.0 M en CH_2Cl_2, 0.5 mL,1.0 mL) y la reacción fue dejada calentar a temperatura ambiente durante la noche. La reacción fue concentrada y el residuo restante fue disuelto en EtOAc. La solución fue separada con una solución de $NaHCO_3$ acuosa saturada y las capas fueron separadas. La fase acuosa fue extractada con EtOAc (3 X) y las fases orgánicas combinadas fueron lavadas con salmuera, secadas ($MgSO_4$), absorbidas a SiO_2 y purificadas por cromatogRafía flash (4:1 hexanes-EtOAc) para dar 2 como un residuo incoloro.

Ejemplo 1110

N1-Metil-4-fenoxibenceno-1,2-diamina

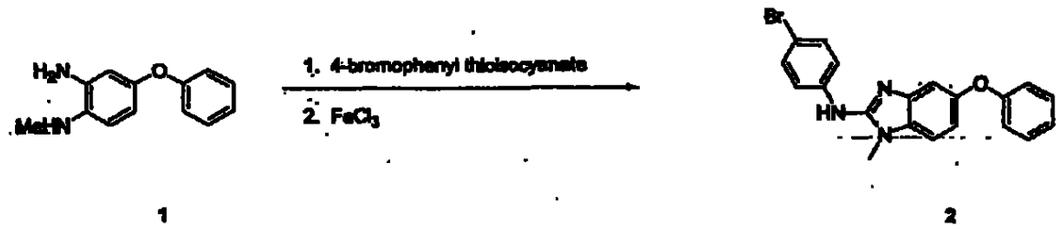


1 2

Hidrazino monohidrato (0.13 mL, 2.7 mmol) fue añadido a una solución de ftalimida 1 (134 mg, 0.39 mmol) en etanol (4 mL). La reacción fue mantenida a temperatura ambiente durante la noche y luego filtrada por medio de Celite. La pasta filtrante fue enjuagada con EtOAc (3 X) y las porciones orgánicas fueron combinadas y concentradas para dar como resultado diamina 2 que fue llevada más adelante sin purificación adicional. LCMS *m/z* 215.1 (MH^+), t_R = 1.77 min.

Ejemplo 1111

Síntesis de (4-Bromofenil)-(1-metil-5-fenoxi-1H-bencimidzol-2-il)-amina



1 2

Bencimidazol 2 fue preparado como el ejemplo 120b: ^{1}H NMR (300 MHz, CD_3OD) δ 7.68 (app ddd, *J*= 2.9, 4.9, 8.8 Hz, 2 H), 7.53 (app d, *J*= 8.8 Hz, 1 H), 7.41 (app ddd, *J*= 2.9, 4.9, 8.8 Hz, 2 H), 7.40 (app ddd, *J*= 1.0, 2.0, 8.5 Hz, 2 H), 7.24 (app ddd, *J*= 1.0, 2.0, 8.5 Hz, 1 H), 7.07 (app dd, *J*= 2.2, 8.8 Hz, 1 H), 7.00 (app d, *J*= 2.2 Hz, 1 H), 7.00 (app ddd, *J*= 1.0, 2.0, 8.5 Hz, 2 H), 3.82 (s, 3 H); LCMS *m/z* 394.0 (MH^+), t_R = 2.36 min.

Ejemplo 1112

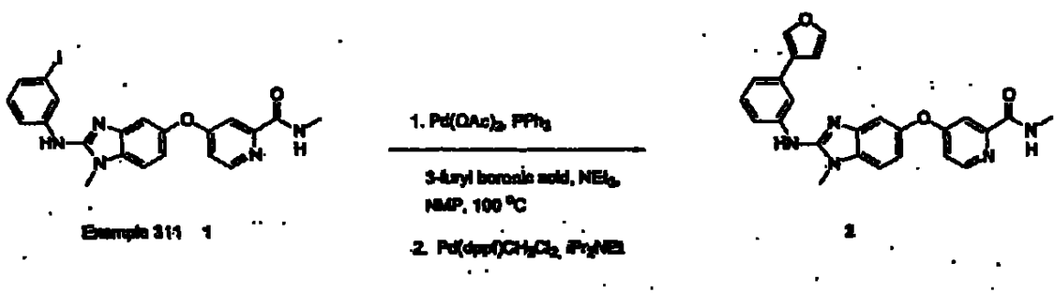


Example 371 1 2

Una solución 1 en MeCN fue tratada con 1 N HCl acuoso y congelado seco. El residuo resultante fue purificado por HPLC fase-reversible para crear un cloruro de vinilo 2 como una sal TFA: LCMS *m/z* 434.2 (MH^+), t_R = 2.48 min.

Ejemplo 1113

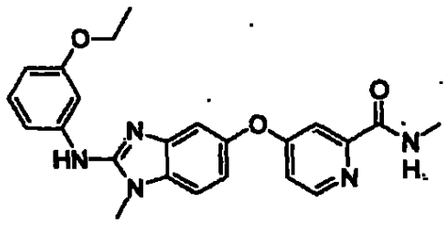
4[2-(3-Furan-3-il-fenilamino)-1-metil-1H-bencimidazol-5-iloxi]-piridin-2-ácido carboxílico metil amida.



Ejemplo 311 1 2

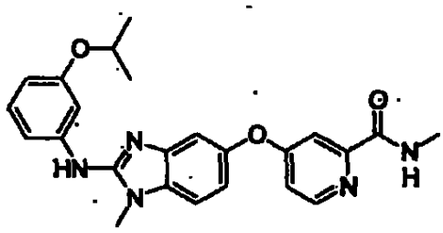
Una solución de $Pd(Oac)_2$ (4.5 mg, 0.02 mmol) y trifenilfosfina (13.1 mg, 0.05 mmol) en NMP seco (1 mL) fue agitada a temperatura ambiente por 20 minutos. Aril ioduro 1 (100 mg, 0.2 mmol), 3-furil ácido borónico (45 mg, 0.4 mmol), y trietilamina (0.11 mL, 0.8 mmol) fueron añadidos y la solución resultante fue degasificada y drenada con Ar. La reacción fue calentada a 100° C por 2 horas; LCMS indica ninguna conversión. La reacción fue dejada enfriar a temperatura ambiente bajo Ar y $Pd(dppf)Cl_2CH_2Cl_2$ y diisopropiletilamina (0.14 mL) fueron añadidos. La reacción fue calentada a 100° C y mantenida durante la noche. La reacción fue dejada enfriar a temperatura ambiente y el LCMS indicaba completa conversión. La reacción fue separada entre la solución $NaHCO_3$ acuosa saturada y EtOAc y la mezcla resultante filtrada por medio de Celite. Los sólidos restantes fueron lavados con agua y EtOAc. Los enjuagues combinados fueron divididos y separados. La fase acuosa fue extraída con EtOAc (3 X) y las porciones orgánicas combinadas fueron lavadas con Na_2CO_3 acuosa saturada y salmuera, secadas ($MgSO_4$) y concentradas. El residuo crudo fue purificado por HPLC fase-reversible para crear 2 como una sal TFA: LCMS *m/z* 440.3 (MH^+), t_R = 2.35 min.

Ejemplo 1114



Preparada como el Ejemplo 120b.

Ejemplo 1115



Preparada como el Ejemplo 120b.

Ejemplo 1116

Raf/Mek Ensayo de Filtración

"Buffers"

Tipo de "buffer": 50Mm Tris, pH 7.5, 15 mM $MgCl_2$, 0.1 mM EDTA, 1mM DTT

"buffer" de lavado: 25mM Hepes, pH 7.4, 50 mM sodio pirofosfato, 500 mM NaCl

Reactivo de parada: 30 mM EDTA

Materiales

Raf, activo:	Upstate Biotech # 14-352
Mek, inactivo:	Upstate Biotech # 14-205

^{33}P-ATP: NEN Perkin Elmer # NEG 602 h

placas de ensayo 96perforaciones: Falcon U-fondo placas de polipropileno #35-1190

Aparatos de filtración: Millipore #MAVM 096 OR

96 placas de filtración perforaciones: Millipore Immobilon 1 #MAIP NOB

Fluido de centellear: Wallac OptiPhase "SuperMix"#1200-439

Condiciones de Ensayo

Raf aproximadamente 120 pM

Mek aproximadamente 60 nM

^{33}p-ATP 100 nM

Tiempos de reacción 45-60 minutos a temperatura ambiente.

Protocolos del Ensayo

Raf y Mek fuero combinados a combinaciones finales 2X in un "buffer" de ensayo (50 mM Tris, pH 7.5, 15 mM $MgCl_2$, 0.1 mM EDTA y 1 mM DTT) y dispensados a 15 µl por perforación en placas de ensayo de polipropileno (Falcon U-Bottom polipropileno placas 96 perforaciones de ensayo #35-1190). Los níveles de fondo son determinados en "wells" conteniendo Mek y DMSO sin Raf.

A los Raf/Mek conteniendo "wells" se les añadió 3 µl de 10X de una prueba del compuesto inhibidor Raf Quinaza en 100% DMSO. La actividad reactora del Raf Quinaza comenzó con la adición de 12 µl por well de 2.5X ^{33}P-ATP diluido en un "buffer" de ensayo. Luego de 45-60 minutos, la reacción fue parada con la adición de 70 µl de reactivo de parada (30 mM EDTA). Los placas de filtración fueron pre-mojadas por 5 minutos con 70% de etanol, y luego enjuagadas por filtración con un "buffer" de lavado. Pruebas (90µl) de las reacciones fueron luego transferidas a las placas perforadas de filtrado. Las placas de filtrado fueron lavadas 6X con "buffer" de lavado usando aparatos de filtración Millipore. Las placas

fueron secadas y 100µl por perforación de fluido de centello (Wallac OptiPhase "SuperMix" #1200-439) fue añadido. El CPM fue luego determinado usando el lector Wallac Microbeta 1450.

Ejemplo 1117

Ensayo 2: Pantalla Raf Biotinilada

Pantalla Raf *In Vitro*

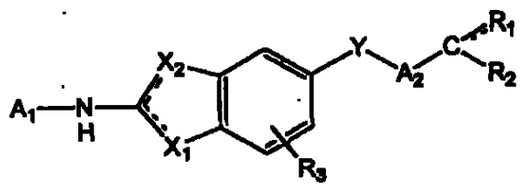
La actividad de varias isoformas de Raf Serino/Treonino Quinaza puede ser medido suministrando ATP, sustrato MEK, y ensayando la transferencia de mitad fosfato al residuo MEK. Los isoformos recombinantes de Raf fueron obtenidos por la purificación de células de insectos infectadas sf9 con un vector de expresión báculode virus recombinante de Raf humano. Un recombinante Quinaza MEK inactivo fue expresado en *E. coli* y clasificados con purificación Biotin post. Para cada ensayo, los compuestos de ensayo fueron diluidos en serie en DMSO y luego mezclados con Raf (0.50 nM) y biotil-MEK Quinaza inactivo (50 nM) en "buffer" de reacción más ATP (1 µM). Las reacciones fueron subsecuentemente incubadas por 2 horas a temperatura ambiente y detenidas por la adición de 0.5 M EDTA. La mezcla de la reacción detenida fue transferida a una placa neutradavin-revestida (Pierce) e incubadas por una hora. El producto fosforilado fue medido con el sistema fluorescente (Wallac) de resolución de tiempo DELFIA, usando una anti-p-MEK de conejo (señalador de células) como el anti-cuerpo primario y una célula marcada "europium" anti-conejo como el anticuerpo secundario. La florescencia de resolución de tiempo se leyó en un fluorómetro Wallac 1232 DELFIA. La concentración de cada compuesto para el 50% de inhibición (IC_{50}) fue calculada por regresión no lineal usando el programa de análisis de datos XLFIT.

Usando los procedimientos de los Ejemplos 1116 o 1117, los compuestos de los Ejemplos 1-1094 demostraron tener una actividad inhibitoria al Raf Quinaza a un IC_{50} de menos de 5μM.

Mientras que las versiones preferidas de la invención han sido ilustradas y descritas, se apreciará que varios cambios podrán ser hechos sin apartarse del espíritu y del alcance de la invensión.

Las versiones del invento en donde una propiedad exclusiva o privilegio es solicitado se definen de la siguiente manera:

1. Un compuesto de Fórmula (I):



(I)

donde, X_1 y X_2 son seleccionados independientemente de = N-,-NR_4, -O-, o –S-, estableciendo que X_1 es –NR_4, -O- o –S-, por consiguiente X_2 es = N-, o si X_2 es –NR_4-, -O- o –S-, entonces X_2 es = N-, y ambos X_1 y X_2 no son = N-; Y es O ó S;

Y es O ó S;

A_1 es alquil sustituido o no sustituido, cicloalquil, heterocicloalquil, aril, aril policíclico, arilalquil policíclico, heteroaril, biaril, heteroarilaril, heteroarilheteroaril, cicloalquilalquil, heterocicloalquilalquil, arilalquil, heteroarilalquil, biarilalquil, o heteroarilarilalquil;

A_2 es heteroaril sustituido o no sustituido;

R_1 es O ó H, y R_2 es NR_5R_6 o hidroxil; o R_1 es tomado junto a R_2 para formar una heterocicloalquil sustituido o no sustituido o un grupo heteroaril; donde, la línea punteada representa un enlace singular o doble;

R_3 es hidrógeno, halógeno, bajoalquil, o bajoalcoxi;

R_4 es hidrógeno, hidroxil, alquilamino, dialquilamino o alquil;

R_5 y R_6 son seleccionados independientemente de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil; o R_5 y R_6 son tomados en conjunto

para formar una heterociclo sustituido o no sustituido o heteroaril; y

las sales farmacéuticamente aceptadas, esteres y prodrogas.

2. Un compuesto de Solicitud 1 donde X es NR_4.

3. Un compuesto de Solicitud 2 donde R_4 es hidrógeno.

4. Un compuesto de Solicitud 2 donde R_4 es metil.

5. Un compuesto de Solicitud 1 donde Y es O.

6. Un compuesto de Solicitud 1 donde A_1 es seleccionado de los grupos consistentes de fenil sustituidos o no sustituidos, piridil, piridinil, fenilalquil, piridilalquil, pirimidinilalquil, heterociclilcarbonifenil, heterociclilfenil, heterociclilalquilfenil, clorofenil, fluorofenil, bromofenil, iodofenil, dihalofenil, nitrofenil, 4-bromofenil, 4-clorofenil, alquilbenzoato, alcoxifenil, dialcoxifenil, dialquilfenil, trialquilfenil, tiofeno, tiofeno-2-carboxilato, alquiltiofenil, trifluorometilfenil, acetilfenil, sulfamoilfenil, bifenil, ciclohexilfenil, feniloxifenil, dialquilaminofenil, alquilbromofenil, alquilclorofenil, alquilfluorofenil, trifluorometilclorofenil, trifluorometilbromofenil, indenil, 2,3-dihidroindenil, tetralinil, trifluorofenil, (trifluorometil)tiofenil, alcoxibifenil, morfolinil, N-piperazinil, N-morfonililalquil, piperazinilalquil, ciclohexilalquil, indolil, 2,3-dihidroindolil, 1-acetil-2,3-dihidroindolil, cicloheptil, biciclo[2.2.1]hept-2-il, hidroxifenil, hidroxialquilfenil, pirrolidinil, pirrolidin-1-il, pirrolidin-1-ilalquil, 4-amino(imino)metilfenil, isoxazolil, indazolil, adamantil, biciclohexil, quinuclinidil, imidazolil, bencimidazolil, imidazolilfenil, fenilimidazolil, ptalamido, naftil, benzofenona, anilinil, anizolil, quinolinil, quinolinonil, fenilsulfonil, fenilalquilsulfonil, 9H-flouren-1-il, piperidin-1-il, piperidin-1-ilalquil, ciclopropil, ciclopropilalquil, pirimidin-5-ilfenil, quinolidinilfenil, furanil, furanilfenil, N-metilpiperidin-4-il, pirrolidin-4-ilpiridinil, 4-diazepan-1-il, hidroxipirrolidin-1-il, dialquilaminopirrilidin-1-il, 1,4'-bipiperidin-1'-il, y (1,4'-bipepiridin-1'-ilcarbonil)fenil.

7. Un compuesto de Solicitud 1 donde A_2 es un piridil sustituido o no sustituido.

8. Un compuesto de Solicitud 1 donde R_1 es O y la línea punteada representa un enlace singular o doble.

9. El compuesto de Solicitud 1 donde R_2 es NR_5R_6, R_5 es hidrógeno y R_6 es seleccionado de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil.

10. Un compuesto de Solicitud 1 donde R_1 es tomado junto con R_2 para formar heterocicloalquil sustituidos o no sustituidos o grupo heteroaril.

11. Un compuesto de Solicitud 1 donde R_3 es un bajoalcoxi.

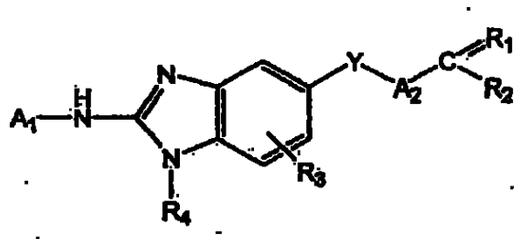
12. Un compuesto de Solicitud 11 donde R_3 es metoxi.

13. Un compuesto de Solicitud 1 donde R_4 es un bajoalquil.

14. Un compuesto de Solicitud 13 donde R_4 es metil.

15. Un compuesto de Solicitud 1 R_1 es O, R_2 es NR_5R_6, R_5 es H, y R_6 es metil.

16. Un compuesto de formula (II):



(II)

donde Y es O ó S;

A_1 es cicloalquil sustituido o no sustituido, heterocicloalquil, aril, aril policíclico, arilalquil policíclico, heteroaril, biaril, heteroarilaril, heteroarilheteroaril, cicloalquilalquil, heterocicloalquilalquil, arilalquil, heteroarilalquil, biarilalquil, o heteroarilarilalquil;

A_2 es heteroaril sustituido o no sustituido;

R_1 es O, y R_2 es NR_5R_6; o R_1 es tomado junto a R_2 para formar un heterocicloalquil sustituido o no sustituido o un grupo heteroaril; donde, la línea punteada representa un enlace singular o doble;

R_3 es hidrógeno, halógeno, bajoalquil, o bajoalcoxi;

R_4 es hidrógeno,o bajoalquil;

R_5 y R_6 son seleccionados independientemente de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil; o R_5 y R_6 son tomados en conjunto para formar una heterociclo sustituido o no sustituido o heteroaril; y

las sales farmacéuticamente aceptadas, ésteres y prodrogas.

17. Un compuesto de Solicitud 16 donde R_4 es hidrógeno

18. Un compuesto de Solicitud 16 donde R_4 es metil.

19. Un compuesto de Solicitud 16 donde Y es O.

20. Un compuesto de Solicitud 16 donde A_1 es seleccionado de los grupos consistentes de fenil sustituidos o no sustituidos, piridil, piridinil, fenilalquil, piridilalquil, pirimidinilalquil, heterociclilcarbonifenil, heterociclilfenil, heterociclilalquilfenil, clorofenil, fluorofenil, bromofenil, iodofenil, dihalofenil, nitrofenil, 4-bromofenil, 4-clorofenil, alquilbenzoato, alcoxifenil, dialcoxifenil, dialquilfenil, trialquilfenil, tiofeno, tiofeno-2-carboxilato, alquiltiofenil, trifluorometilfenil, acetilfenil, sulfamoilfenil, bifenil, ciclohexilfenil, feniloxifenil, dialquilaminofenil, alquilbromofenil, alquilclorofenil, alquilfluorofenil, trifluorometilclorofenil, trifluorometilbromofenil, indenil, 2,3-dihidroindenil, tetralinil, trifluorofenil, (trifluorometil)tiofenil, alcoxibifenil, morfolinil, N-piperazinil, N-morfonililalquil, piperazinilalquil, ciclohexilalquil, indolil, 2,3-dihidroindolil, 1-acetil-2,3-dihidroindolil, cicloheptil, biciclo[2.2.1]hept-2-il, hidroxifenil, hidroxialquilfenil, pirrolidinil,

pirrolidin-1-il, pirrolidin-1-ilalquil, 4-amino(imino)metilfenil, isoxazolil, indazolil, adamantil, biciclohexil, quinuclinidil, imidazolil, bencimidazolil, imidazolilfenil, fenilimidazolil, ptalamido, naftil, benzofenona, anilinil, anizolil, quinolinil, quinolinonil, fenilsulfonil, fenilalquilsulfonil, 9H-flouren-1-il, piperidin-1-il, piperidin-1-ilalquil, ciclopropil, ciclopropilalquil, pirimidin-5-ilfenil, quinolidinilfenil, furanil, furanilfenil, N-metilpiperidin-4-il, pirrolidin-4-ilpiridinil, 4-diazepan-1-il, hidroxipirrolidin-1-il, dialquilaminopirrilidin-1-il, 1,4'-bipiperidin-1'-il, y (1,4'-bipepiridin-1'-ilcarbonil)fenil.

21. Un compuesto de Solicitud 16 donde A_2 es un piridil sustituido o no sustituido.

22. Un compuesto de Solicitud 16 donde R_1 es O y la línea punteada representa un enlace singular o doble.

23. El compuesto de Solicitud 16 donde R_2 es NR_5R_6, R_5 es hidrógeno y R_6 es seleccionado de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil.

24. Un compuesto de Solicitud 16 donde R_1 es tomado junto con R_2 para formar heterocicloalquil sustituidos o no sustituidos o grupo heteroaril.

25. Un compuesto de Solicitud 16 donde R_1 es O, R_2 es NR_5R_6, R_5 es H y R_6 es metil

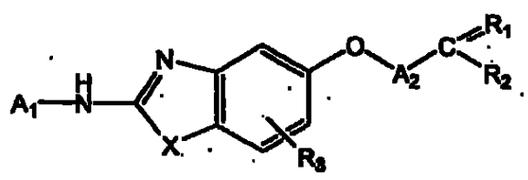
26. Un compuesto de Solicitud 16 donde R_3 es bajoalcoxi

27. Un compuesto de Solicitud 26 donde R_3 es un metoxi.

28. Un compuesto de Solicitud 16 donde R_4 es bajoalquil.

29. Un compuesto de Solicitud 28 donde R_4 es metil.

30. Un compuesto de fórmula (III):



(III)

donde X es NR_4, O ó S;

A_1 es cicloalquil sustituido o no sustituido, heterocicloalquil, aril, aril policíclico, arilalquil policíclico, heteroaril, biaril, heteroarilaril, heteroarilheteroaril, cicloalquilalquil, heterocicloalquilalquil, arilalquil, heteroarilalquil, biarilalquil, o heteroarilarilalquil;

A_2 es heteroaril sustituido o no sustituido;

R_1 es O, y R_2 es NR_5R_6; o R_1 es tomado junto a R_2 para formar un heterocicloalquil sustituido o no sustituido o un grupo heteroaril; donde, la línea punteada representa un enlace singular o doble;

R_3 es hidrógeno, halógeno, bajoalquil, o bajoalcoxi;

R_4 es hidrógeno,o bajoalquil;

R_5 y R_6 son seleccionados independientemente de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil; o R_5 y R_6 son tomados en conjunto para formar una heterociclo sustituido o no sustituido o heteroaril; y

las sales farmacéuticamente aceptadas, esters y prodrogas.

31. Un compuesto de Solicitud 30 donde X es NR_4.

32. Un compuesto de Solicitud 31 donde R_4 es hidrógeno.

33. Un compuesto de Solicitud 30 donde R_4 es metil.

34. Un compuesto de Solicitud 30 donde A_1 es seleccionado de los grupos consistentes de fenil sustituidos o no sustituidos, piridil, piridinil, fenilalquil, piridilalquil, pirimidinilalquil, heterociclilcarbonifenil, heterociclilfenil, heterociclilalquilfenil, clorofenil, fluorofenil,

bromofenil, iodofenil, dihalofenil, nitrofenil, 4-bromofenil, 4-clorofenil, alquilbenzoato, alcoxifenil, dialcoxifenil, dialquilfenil, trialquilfenil, tiofeno, tiofeno-2-carboxilato, alquiltiofenil, trifluorometilfenil, acetilfenil, sulfamoilfenil, bifenil, ciclohexilfenil, feniloxifenil, dialquilaminofenil, alquilbromofenil, alquilclorofenil, alquilfluorofenil, trifluorometilclorofenil, trifluorometilbromofenil, indenil, 2,3-dihidroindenil, tetralinil, trifluorofenil, (trifluorometil)tiofenil, alcoxibifenil, morfolinil, N-piperazinil, N-morfonililalquil, piperazinilalquil, ciclohexilalquil, indolil, 2,3-dihidroindolil, 1-acetil-2,3-dihidroindolil, cicloheptil, biciclo[2.2.1]hept-2-il, hidroxifenil, hidroxialquilfenil, pirrolidinil, pirrolidin-1-il, pirrolidin-1-ilalquil, 4-amino(imino)metilfenil, isoxazolil, indazolil, adamantil, biciclohexil, quinuclinidil, imidazolil, bencimidazolil, imidazolilfenil, fenilimidazolil, ptalamido, naftil, benzofenona, anilinil, anizolil, quinolinil, quinolinonil, fenilsulfonil, fenilalquilsulfonil, 9H-flouren-1-il, piperidin-1-il, piperidin-1-ilalquil, ciclopropil, ciclopropilalquil, pirimidin-5-ilfenil, quinolidinilfenil, furanil, furanilfenil, N-metilpiperidin-4-il, pirrolidin-4-ilpiridinil, 4-diazepan-1-il, hidroxipirrolidin-1-il, dialquilaminopirrilidin-1-il, 1,4'-bipiperidin-1'-il, y (1,4'-bipepiridin-1'-ilcarbonil)fenil.

35. Un compuesto de Solicitud 30 donde A_2 es un piridil sustituido o no sustituido.

36. Un compuesto de Solicitud 30 donde R_1 es O y la línea punteada representa un enlace singular o doble.

37. Un compuesto de Solicitud 30 donde R_2 es NR_5R_6, R_5 es hidrógeno y R_6 es seleccionado de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil.

38. Un compuesto de Solicitud 30 donde R_1 es tomado junto con R_2 para formar heterocicloalquil sustituidos o no sustituidos o grupo heteroaril.

39. Un compuesto de Solicitud 30 donde R_4 es bajo-alcoxi.

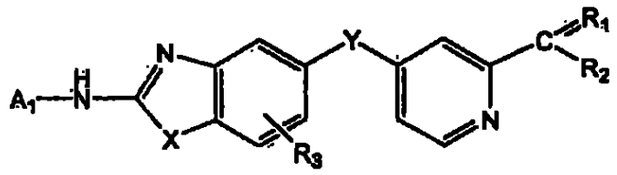
40. Un compuesto de Solicitud 39 donde R_3 es metoxi.

41. Un compuesto de Solicitud 30 donde R_4 es bajo-alquil.

42. Un compuesto de Solicitud 41 donde R_4 es metil.

43. Un compuesto de Solicitud 30 donde R_1 es O, R_2 es NR_5R_6, R_5 es H y R_6 es metil.

44. Un compuesto de fórmula (IV):



(IV)

donde X es NR_4, O ó S;

Y es O ó S;

A_1 es cicloalquil sustituido o no sustituido, heterocicloalquil, aril, aril policíclico, arilalquil policíclico, heteroaril, biaril, heteroarilaril, heteroarilheteroaril, cicloalquilalquil, heterocicloalquilalquil, arilalquil, heteroarilalquil, biarilalquil, o heteroarilarilalquil;

R_1 es O, y R_2 es NR_5R_6; o R_1 es tomado junto a R_2 para formar un heterocicloalquil sustituido o no sustituido o un grupo heteroaril; donde, la línea punteada representa un enlace singular o doble;

R_3 es hidrógeno, halógeno, bajo-alquil, o bajo-alcoxi;

R_4 es hidrógeno,o bajo-alquil;

R_5 y R_6 son seleccionados independientemente de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil; o R_5 y R_6 son tomados en conjunto para formar una heterociclo sustituido o no sustituido o heteroaril; y

las sales farmacéuticamente aceptadas, esters y prodrogas.

45. Un compuesto de Solicitud 44 donde X es NR_4.

46. Un compuesto de Solicitud 45 donde R_4 es hidrógeno.

47. Un compuesto de Solicitud 45 donde R_4 es metil.

48. Un compuesto de Solicitud 44 donde Y es O

49. Un compuesto de Solicitud 44 donde A_1 es seleccionado de los grupos consistentes de fenil sustituidos o no sustituidos, piridil, piridinil, fenilalquil, piridilalquil, pirimidinilalquil, heterociclilcarbonifenil, heterociclilfenil, heterociclilalquilfenil, clorofenil, fluorofenil, bromofenil, iodofenil, dihalofenil, nitrofenil, 4-bromofenil, 4-clorofenil, alquilbenzoato, alcoxifenil, dialcoxifenil, dialquilfenil, trialquilfenil, tiofeno, tiofeno-2-carboxilato, alquiltiofenil, trifluorometilfenil, acetilfenil, sulfamoilfenil, bifenil, ciclohexilfenil, feniloxifenil, dialquilaminofenil, alquilbromofenil, alquilclorofenil, alquilfluorofenil, trifluorometilclorofenil, trifluorometilbromofenil, indenil, 2,3-dihidroindenil, tetralinil, trifluorofenil, (trifluorometil)tiofenil, alcoxibifenil, morfolinil, N-piperazinil, N-morfonililalquil, piperazinilalquil, ciclohexilalquil, indolil, 2,3-dihidroindolil, 1-acetil-2,3-dihidroindolil, cicloheptil, biciclo[2.2.1]hept-2-il, hidroxifenil, hidroxialquilfenil, pirrolidinil, pirrolidin-1-il, pirrolidin-1-ilalquil, 4-amino(imino)metilfenil, isoxazolil, indazolil, adamantil, biciclohexil, quinuclinidil, imidazolil, bencimidazolil, imidazolilfenil, fenilimidazolil, ptalamido, naftil, benzofenona, anilinil, anizolil, quinolinil, quinolinonil, fenilsulfonil, fenilalquilsulfonil, 9H-flouren-1-il, piperidin-1-il, piperidin-1-ilalquil, ciclopropil, ciclopropilalquil, pirimidin-5-ilfenil, quinolidinilfenil, furanil, furanilfenil, N-metilpiperidin-4-il, pirrolidin-4-ilpiridinil, 4-diazepan-1-il, hidroxipirrolidin-1-il, dialquilaminopirrilidin-1-il, 1,4'-bipiperidin-1'-il, y (1,4'-bipepiridin-1'-ilcarbonil)fenil.

50. Un compuesto de Solicitud 44 donde R_1 es O y la línea punteada representa un

enlace singular o doble.

51. Un compuesto de Solicitud 44 donde R_2 es NR_5R_6, R_5 es hidrógeno y R_6 es seleccionado de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil.

52. Un compuesto de Solicitud 44 donde R_1 es tomado junto con R_2 para formar heterocicloalquil sustituidos o no sustituidos o grupo heteroaril.

53. Un compuesto de Solicitud 44 donde R_3 es bajoalcoxi.

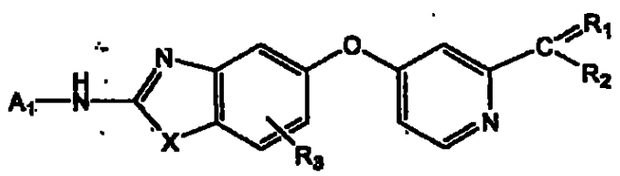
54. Un compuesto de Solicitud 53 donde R_3 es metoxi.

55. Un compuesto de Solicitud 44 donde R_4 es bajoalquil.

56. Un compuesto de Solicitud 55 donde R_4 es metil.

57. Un compuesto de Solicitud 44 donde R_1 es O, R_2 es NR_5R_6, R_5 es H y R_6 es metil.

58. Un compuesto de fórmula (V):



(V)

donde X es NR_4, O ó S;

A_1 es cicloalquil sustituido o no sustituido, heterocicloalquil, aril, aril policíclico, arilalquil policíclico, heteroaril, biaril, heteroarilaril, heteroarilheteroaril, cicloalquilalquil, heterocicloalquilalquil, arilalquil, heteroarilalquil, biarilalquil, o heteroarilarilalquil;

R_1 es O, y R_2 es NR_5R_6; o R_1 es tomado junto a R_2 para formar un heterocicloalquil sustituido o no sustituido o un grupo heteroaril; donde, la línea punteada representa un enlace singular o doble;

R_3 es hidrógeno, halógeno, bajo-alquil, o bajo-alcoxi;

R_4 es hidrógeno, o bajo-alquil;

R_5 y R_6 son seleccionados independientemente de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil; o R_5 y R_6 son tomados en conjunto para formar una heterociclo sustituido o no sustituido o heteroaril; y

las sales farmacéuticamente aceptadas, esters y prodrogas.

59. Un compuesto de Solicitud 58 donde X es NR_4.

60. Un compuesto de Solicitud 59 donde R_4 es hidrógeno.

61. Un compuesto de Solicitud 59 donde R_4 es metil.

62. Un compuesto de Solicitud 58 donde A_1 es seleccionado de los grupos consistentes de fenil sustituidos o no sustituidos, piridil, piridinil, fenilalquil, piridilalquil, pirimidinilalquil, heterociclilcarbonifenil, heterociclilfenil, heterociclilalquilfenil, clorofenil, fluorofenil, bromofenil, iodofenil, dihalofenil, nitrofenil, 4-bromofenil, 4-clorofenil, alquilbenzoato, alcoxifenil, dialcoxifenil, dialquilfenil, trialquilfenil, tiofeno, tiofeno-2-carboxilato, alquiltiofenil, trifluorometilfenil, acetilfenil, sulfamoilfenil, bifenil, ciclohexilfenil, feniloxifenil, dialquilaminofenil, alquilbromofenil, alquilclorofenil, alquilfluorofenil, trifluorometilclorofenil, trifluorometilbromofenil, indenil, 2,3-dihidroindenil, tetralinil, trifluorofenil, (trifluorometil)tiofenil, alcoxibifenil, morfolinil, N-piperazinil, N-morfonililalquil, piperazinilalquil, ciclohexilalquil, indolil, 2,3-dihidroindolil, 1-acetil-2,3-dihidroindolil, cicloheptil, biciclo[2.2.1]hept-2-il, hidroxifenil, hidroxialquilfenil, pirrolidinil, pirrolidin-1-il, pirrolidin-1-ilalquil, 4-amino(imino)metilfenil, isoxazolil, indazolil, adamantil, biciclohexil, quinuclinidil, imidazolil, bencimidazolil, imidazolilfenil, fenilimidazolil, ptalamido, naftil, benzofenona, anilinil, anizolil, quinolinil, quinolinonil, fenilsulfonil, fenilalquilsulfonil, 9H-flouren-1-il, piperidin-1-il, piperidin-1-ilalquil, ciclopropil,

ciclopropilalquil, pirimidin-5-ilfenil, quinolidinilfenil, furanil, furanilfenil, N-metilpiperidin-4-il, pirrolidin-4-ilpiridinil, 4-diazepan-1-il, hidroxipirrolidin-1-il, dialquilaminopirrilidin-1-il, 1,4'-bipiperidin-1'-il, y (1,4'-bipepiridin-1'-ilcarbonil)fenil.

63. Un compuesto de Solicitud 58 donde R_1 es O y la línea punteada representa un enlace singular o doble.

64. Un compuesto de Solicitud 58 donde R_2 es NR_5R_6, R_5 es hidrógeno y R_6 es seleccionado de hidrógeno, y alquil sustituidos o no sustituidos, alcoxialquil, aminoalquil, amidoalquil, acil, cicloalquil, heterocicloalquil, aril, heteroaril, alquiloxialquilheterociclo, y heteroarilalquil.

65. Un compuesto de Solicitud 58 donde R_1 es tomado junto con R_2 para formar heterocicloalquil sustituidos o no sustituidos o grupo heteroaril.

66. Un compuesto de Solicitud 58 donde R_3 es bajoalcoxi.

67. Un compuesto de Solicitud 66 donde R_3 es metoxi.

68. Un compuesto de Solicitud 58 donde R_4 es bajoalquil.

69. Un compuesto de Solicitud 68 donde R_4 es metil.

70. Un compuesto de Solicitud 58 donde R_1 es O, R_2 es NR_5R_6, R_5 es H y R_6 es metil.

71. Una composición comprendiendo una cantidad de un compuesto de Solicitud 1, 16, 30, 44, ó 58 efectivos para inhibir la actividad Raf en un sujeto humano o animal cuando le es administrada esta composición junto con un portador farmacéuticamente aceptable.

72. Una composición de la Solicitud 71 que incluye adicionalmente al menos un agente adicional para el tratamiento del cáncer.

73. Una composición de Solicitud 72 en donde al menos un agente adicional para el tratamiento del cáncer es seleccionado de irinotecano, topotecano, gemcitabino, 5-fluorouracil, carboplatino leucovorino, cisplatino, taxanos, tezacitabino, ciclofosfamida, alcaloides vinca,

imatinib, antraciclinos, rituximab y trastuzumab.

74. Un método de inhibir la actividad Raf Quinaza en un sujeto animal o humano, se compone de la administración a un sujeto humano o animal de un compuesto conteniendo una cantidad de Solicitud 1, 16, 30, 44 ó 58 efectivo para inhibir la actividad Raf Quinaza en sujetos humanos o animales.

75. Un método para el tratamiento del cáncer en sujetos animales o humanos, se compone de la administración a un sujeto humano o animal de un compuesto conteniendo una cantidad de Solicitud 1, 16, 30, 44 ó 58 efectivo para inhibir la actividad Raf Quinaza en sujetos humanos o animales.

76. Un método de Solicitud 75 que contiene adicionalmente administrar a sujetos humanos o animales al menos un agente adicional para el tratamiento del cáncer.

77. Una composición de Solicitud 76 en donde al menos un agente adicional para el tratamiento del cáncer es seleccionado de irinotecano, topotecano, gemcitabino, 5-fluorouracil, carboplatino leucovorino, cisplatino, taxanos, tezacitabino, ciclofosfamida, alcaloides vinca, imatinib, antraciclinos, rituximab y trastuzumab.

78. Un método para el tratamiento del cáncer dependiente de hormonas en un sujeto humano o animal, se compone de la administración a un sujeto humano o animal de un compuesto conteniendo una cantidad de Solicitud 1, 16, 30, 44 ó 58 efectivo para inhibir la actividad Raf Quinaza en sujetos humanos o animales.

79. Un método de Solicitud 78 donde un cáncer dependiente de hormonas es cáncer de mamas o cáncer de próstata.

80. Un método de Solicitud 78 que incluye la administración a un sujeto humano o animal de al menos un agente adicional para el tratamiento del cáncer.

81. Una composición de Solicitud 80 en donde al menos un agente adicional para el

tratamiento del cáncer es seleccionado de irinotecano, topotecano, gemcitabino, 5-fluorouracil, carboplatino leucovorino, cisplatino, taxanos, tezacitabino, ciclofosfamida, alcaloides vinca, imatinib, antraciclinos, rituximab y trastuzumab.

82. Un método para el tratamiento del cáncer hematológico en un sujeto humano o animal, se compone de la administración a un sujeto humano o animal de un compuesto conteniendo una cantidad de Solicitud 1, 16, 30, 44 ó 58 efectivo para inhibir la actividad Raf Quinaza en sujetos humanos o animales.

83. Un método de Solicitud 82 que incluye la administración a un sujeto humano o animal de al menos un agente adicional para el tratamiento del cáncer.

84. Una composición de Solicitud 83 en donde al menos un agente adicional para el tratamiento del cáncer es seleccionado de irinotecano, topotecano, gemcitabino, 5-fluorouracil, carboplatino leucovorino, cisplatino, taxanos, tezacitabino, ciclofosfamida, alcaloides vinca, imatinib, antraciclinos, rituximab y trastuzumab.

85. Un compuesto Solicitud 1, 16, 30, 44 ó 58 para el uso en el tratamiento del cáncer.

86. Un compuesto Solicitud 1, 16, 30, 44 ó 58 en la manufactura de los medicamentos para el tratamiento del cáncer.

PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CHIR-1-20868	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/10117	International filing date (day/month/year) 31 March 2003 (31.03.2003)	Priority date (day/month/year) 29 March 2002 (29.03.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/41; C07D 401/12, 401/14, 405/14, 409/14, 417/12, 417/14 and US Cl.: 514/333, 338, 318, 234.5, 253.09; 544/124, 295, 364; 546/194, 273.4,256		
Applicant CHIRON CORPORATION		

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

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

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

   These annexes consist of a total of 0 sheets.

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

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

Date of submission of the demand	Date of completion of this report
18 September 2003 (18.09.2003)	15 June 2004 (15.06.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Laura L. Stockton, Ph.D. Janice Ford for Telephone No. 703/308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/10117

431

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-241 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 242-254, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____, which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-86	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-86	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-86	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-86 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the compounds and methods of using the compounds as instantly claimed.

WO 00/02778 was listed as an X reference. Example 572 on page 209 of the WO was especially indicated. However, Example 572 has a -NH- group linking the benzimidazole ring to the thiazole ring. The instant claimed compounds have either an oxygen or sulfur (see the definition of the Y variable in the claims) linking the benzimidazole ring to a heteroaryl ring, such as a thiazole ring. Therefore, the WO is considered the state of the art.

NEW CITATIONS

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/41 C07D401/12 C07D405/14 C07D409/14 C07D401/14
C07D417/12 C07D417/14 C07D413/14 C07D407/14 C07D413/12
C07D471/08 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 62778 A (BRISTOL MYERS SQUIBB CO) 26 October 2000 (2000-10-26) see example 572 on page 209	1
A	WO 01 66539 A (STEADMAN JON GRAHAM ;SMITHKLINE BEECHAM PLC (GB); TAKLE ANDREW KEN) 13 September 2001 (2001-09-13) the whole document	1-35

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 2003	15/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bérillon, L

5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/10117

434

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 74-84 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0062778 A	26-10-2000	AU 4233800 A	02-11-2000
		BR 0009721 A	13-02-2002
		CA 2366932 A1	26-10-2000
		CN 1348370 T	08-05-2002
		CZ 20013677 A3	12-06-2002
		EP 1169038 A1	09-01-2002
		HU 0202708 A2	28-12-2002
		JP 2002542193 T	10-12-2002
		NO 20014970 A	10-12-2001
		NZ 513639 A	28-09-2001
		PL 351126 A1	24-03-2003
		TR 200102969 T2	21-08-2002
		WO 0062778 A1	26-10-2000
WO 0166539 A	13-09-2001	AU 3583801 A	17-09-2001
		EP 1263753 A1	11-12-2002
		WO 0166539 A1	13-09-2001

with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line

IPEA/ US

PCT

CHAPTER II

435

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 18773.003

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US03/10117	31 March 2003 (31.03.03)	29 March 2003 (29.03.02)

Title of invention
Substituted Benz-azoles and Methods of Their Use as Inhibitors of RAF Kinase

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHIRON CORPORATION
4560 Horton Street
Emeryville, CA 94608
United States of America

Telephone No.: 510.655.8730
Facsimile No.: 510.655.3542
Teleprinter No.: N/A
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RENHOWE, Paul A.
262 Stetson Drive
Danville, CA 94506
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAMURTHY, Savithri
1151 Maggie Lane
Walnut Creek, CA 94597
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

[x] Further applicants are indicated on a continuation sheet.

International application No.
PCT/US03/10117

Continuation of Box No. II APPLICANT(S)

A36

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

AMIRI, Payman
1025 Lizann Drive
Lafayette, CA 94549
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LEVINE, Barry Haskell
1142 Brown Avenue
Lafayette, CA 94549
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

POON, Daniel J.
415 Lagunitas Avenue, #103
Oakland, CA 94610
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SUBRAMANIAN, Sharadha
1061 Harness Circle, #30
San Ramon, CA 94583
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	US

[X] Further applicants are indicated on another continuation sheet.

International application No.
PCT/US03/10117

437

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SUNG, Leonard
118 Amherst Court
Irvine, CA 92612
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FANTL, Wendy
35 Hancock Street
San Francisco, CA 94114
U.S.A.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
UK	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/US03/10117

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE 438

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s) /common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official The address must include postal code and name of country.)*

SUH, Young J.
Chiron Corporation
Intellectual Property
PO Box 8097
Emeryville, CA 94662-8097

Telephone No.
510.923.2706

Facsimile No.
510.655.3542

Teleprinter No.
N/A

Agent's registration No. with the Office
41,337

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed.

the description
☐ as originally filed
☐ as amended under Article 34

the claims
☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings
☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

International application No.
PCT/US03/10117

Box No. VI CHECK LIST

439.

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Young J. Sun
Assistant Secretary
CHIRON CORPORATION

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

440

Annex to the Demand

International application No. PCT/US03/10117	For International Preliminary Examining Authority use only
Applicant's or agent's file reference PP 18773.003	Date stamp of the IPEA
Applicant Chiron Corporation	

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	490.00	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	146.00	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	636.00 TOTAL		

MODE OF PAYMENT

[X]	authorization to charge deposit account with the IPEA (see below)	[ ]	cash
[X]	cheque	[ ]	revenue stamps
[ ]	postal money order	[ ]	coupons
[ ]	bank draft	[ ]	other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ US

[ ] Authorization to charge the total fees indicated above.

[X] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 03-1664

Date: September 18, 2003

Name: Young J. Suh

Signature:

INTERNATIONAL SEARCH REPORT

PCT/US 03/10117

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/41 C07D401/12 C07D405/14 C07D409/14 C07D401/14
C07D417/12 C07D417/14 C07D413/14 C07D407/14 C07D413/12
C07D471/08 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 62778 A (BRISTOL MYERS SQUIBB CO) 26 October 2000 (2000-10-26) see example 572 on page 209	1
A	WO 01 66539 A (STEADMAN JON GRAHAM ;SMITHKLINE BEECHAM PLC (GB); TAKLE ANDREW KEN) 13 September 2001 (2001-09-13) the whole document	1-35

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 2003	15/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bérillon, L

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-70 relate to compounds defined by reference to a desirable characteristic or property, namely prodrugs of formula (I). The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I), pharmaceutically salts and esters thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No.	
International Filing Date	4-22
Name of receiving Office and "PCT International Application"	

Applicant's or agent's file reference *(if desired) (12 characters maximum)*: CHIR-1-20868

Box No. I TITLE OF INVENTION

SUBSTITUTED BENZ-AZOLES AND METHODS OF THEIR USE AS INHIBITORS OF RAF KINASE

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CHIRON CORPORATION
4560 Horton Street
Emeryville, CA 94608-2916
US

Telephone No.: 510.655.8730
Facsimile No.: 510.655.3542
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RENHOWE, Paul A.
282 Stetson Drive
Danville, CA 94506
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SHELTON, Dennis K.
Christensen O'Connor Johnson Kindness PLLC
1420 Fifth Avenue, Suite 2800
Seattle, WA 98101
US

Telephone No.: 206.682.8100
Facsimile No.: 206.224.0779
Teleprinter No.:
Agent's registration No. with the Office: 28,997

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S) 443

If none of the following sub-boxes is used, this sheet should not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RAMURTHY, Savithri
1151 Maggie Lane
Walnut Creek, CA 94597
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AMIRI, Payman
1025 Lizann Drive
Lafayette, CA 94549
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LEVINE, Barry Haskell
1142 Brown Avenue
Lafayette, CA 94549
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

POON, Daniel J.
415 Lagunitas Avenue, #103
Oakland, CA 94610
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S) 444

If none of the following sub-boxes is used, this sheet should not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SUBRAMANIAN, Sharadha
1061 Harness Circle, #30
San Ramon, CA 94583
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SUNG, Leonard
118 Amherst Court
Irvine, CA 92612
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FANTL, Wendy
36 Hancock Street
San Francisco, CA 94114
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: UK

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a): 445

Regional Patent

☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(If other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of

☒ **EP** European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(If other kind of protection or treatment desired, specify on dotted line* .....

National Patent *(If other kind of protection or treatment desired, specify on dotted line):*

☒ AE	United Arab Emirates	☒ GM	Gambia	☒ NZ	New Zealand
☒ AG	Antigua and Barbuda	☒ HR	Croatia	☒ OM	Oman
☒ AL	Albania	☒ HU	Hungary	☒ PH	Philippines
☒ AM	Armenia	☒ ID	Indonesia	☒ PL	Poland
☒ AT	Austria	☒ IL	Israel	☒ PT	Portugal
☒ AU	Australia	☒ IN	India	☒ RO	Romania
☒ AZ	Azerbaijan	☒ IS	Iceland	☒ RU	Russian Federation
☒ BA	Bosnia and Herzegovina	☒ JP	Japan		
☒ BB	Barbados	☒ KE	Kenya	☒ SC	Seychelles
☒ BG	Bulgaria	☒ KG	Kyrgyzsta	☒ SD	Sudan
☒ BR	Brazil	☒ KP	Democratic People's Republic	☒ SE	Sweden
☒ BY	Belarus		of Korea	☒ SG	Singapore
☒ BZ	Belize	☒ KR	Republic of Korea	☒ SK	Slovakia
☒ CA	Canada	☒ KZ	Kazakhstan	☒ SL	Sierra Leone
☒ CH & LI	Switzerland and Liechtenstein	☒ LC	Saint Lucia	☒ TJ	Tajikistan
☒ CN	China	☒ LK	Sri Lanka	☒ TM	Turkmenistan
☒ CO	Colombia	☒ LR	Liberia	☒ TN	Tunisia
☒ CR	Costa Rica	☒ LS	Lesotho	☒ TR	Turkey
☒ CU	Cuba	☒ LT	Lithuania	☒ TT	Trinidad and Tobago
☒ CZ	Czech Republic	☒ LU	Luxembourg		
☒ DE	Germany	☒ LV	Latvia	☒ TZ	United Republic of Tanzania
☒ DK	Denmark	☒ MA	Morocco	☒ UA	Ukraine
☒ DM	Dominica	☒ MD	Republic of Moldova	☒ UG	Uganda
☒ DZ	Algeria			☒ US	United States of America
☒ EC	Ecuador	☒ MG	Madagascar		
☒ EE	Estonia	☒ MK	The former Yugoslav Republic of	☒ UZ	Uzbekistan
☒ ES	Spain		Macedonia	☒ VC	Saint Vincent and the Grenadines
☒ FI	Finland	☒ MN	Mongolia	☒ VN	Viet Nam
☒ GB	United Kingdom	☒ MW	Malawi	☒ YU	Yugoslavia
☒ GD	Grenada	☒ MX	Mexico	☒ ZA	South Africa
☒ GE	Georgia	☒ MZ	Mozambique	☒ ZM	Zambia
☒ GH	Ghana	☒ NO	Norway	☒ ZW	Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ all states that have been bound by...	☐	☐	
☐ the PCT after issuance of this sheet.	☐	☐	

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed: 446

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
Item (1) 29 March 2002 29.03.2002	60/369,068	US		
Item (2)				
Item (3)				
Item (4)				
Item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* .....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA/ EP.....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) In paper form, the following number of sheets:

request (including declaration sheets)	:	6
description (including sequence listings and/or tables related thereto)	:	241
claims	:	13
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	261
sequence listings	:	
tables related thereto	:	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)	:	
Total number of sheets	:	261

(b) ☐ only in computer readable form (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ also in computer readable form (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
1. ☒ fee calculation sheet	447 1
2. ☐ original separate power of attorney	:
3. ☐ original general power of attorney	:
4. ☐ copy of general power of attorney; reference number, if any:	:
5. ☐ statement explaining lack of signature	:
6. ☐ priority document(s) identified in Box No. VI as item(s):	:
7. ☐ translation of international application into *(language)*:	:
8. ☐ separate indications concerning deposited microorganism or other biological material	:
9. ☐ sequence listings in computer readable form *(indicate type and number of carriers)*	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left	:
10. ☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*	
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:
11. ☒ other *(specify)*: Transmittal, Check, and Postcard	: 3

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Dennis K. Shelton, Agent

For receiving Office use only

1. Date of actual receipt of the purported international application:

2. Drawings:
- ☐ received:
- ☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA/

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No. 448

Date stamp of the receiving Office

Applicant's or agent's file reference: CHIR-1-20868

Applicant: CHIRON CORPORATION et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE ..... 240.00 T

2. SEARCH FEE ..... 936.00 S

International search to be carried out by ISA/EP

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) and/or (c) of Box No. IX apply, enter Sub-total number of sheets
Where item (b) and (c) of Box No. IX do not apply, enter Total number of sheets } 261

b1 first 30 sheets 407.00 b1

b2 231 (number of sheets in excess of 30) x 9.00 (fee per sheet) = 2,079.00 b2

b3 additional component (only if sequence listings and/or tables related thereto are filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ b3

Add amounts entered at b1, b2 and b3 and enter total at B ... 2,486.00 B

Designation Fees

The international application contains 5+ designations.

5 (number of designation fees payable *(maximum 5)*) x 88.00 (amount of designation fee) = 440.00 D

Add amounts entered at B and D and enter total at I ..... 2,926.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the

4. FEE FOR PRIORITY DOCUMENT *(If applicable)* ..... 20.00 P

5. TOTAL FEES PAYABLE ..... 4,122.00 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons

☒ cheque ☐ bank draft ☐ revenue stamps ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ US

☐ Authorization to charge the total fees indicated above.

Deposit Account No.: 03-1740

☒ *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Date: 31 March 2003

Name: Dennis K. Shelton, Reg. No. 28,897

☒ Authorization to charge the fee for priority document.

Signature: Dennis K Shelton

447

449

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
Indicación de que se solicita la concesión de una patente	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
Descripción de la invención	( )	( )
Dibujos de ser estos pertinentes.	( )	( )
Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )
DISEÑO INDUSTRIAL ( )		
Indicación de que se solicita el registro de Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )
ESQUEMA DE TRAZADO ( )		
Indicación de que solicita el registro de un Esquema de trazado	( )	( )
Datos de identificación del solicitante o de la persona que presenta La solicitud	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable

Fecha

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04196715 00000000 Folios 446
Fecha (AMD): 2004-10-28 16:40 37
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

448
450

Industria y Comercio
SUPERINTENDENCIA

2020

Bogotá D C

Doctor(a)
DILIA MARIA RODRÍGUEZ D'ALEMAN
Apoderado(a)
CHIRON CORPORATION

REFERENCIA:	Radicación N°	**04-108715**
	Solicitud internacional	**PCT/US03/10117**
	Fecha inicio fase nacional	**2004-10-29**
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

10870

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
26 NOV. 2004
202063

P-586

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

Doctor(a) A
DILIA MARÌA RODRIGUEZ D'ALEMAN
Apoderado(a)
CHIRON CORPORATION

REFERENCIA:	Radicación Nº	**04-108715**
	Solicitud internacional	**PCT/US03/10117**
	Fecha inicio fase nacional	**2004-10-29**
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

11133

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, mediante oficio No **10870** notificado por fijación en lista de fecha **26 de n viembre de 2004**, requirió al doctor(a) **DILIA MARÌA RODRIGUEZ D'ALEMAN** para que complementara la solicitud de acuerdo con las normas citadas.

Sin embargo el mencionado requerimiento no cumplió con los presupuestos establecidos en el artículo 39 de la Decisión 486, es decir no se indicó al solicitante el plazo en el cual se debía presentar la respuesta al mismo, por lo que es procedente revocar en su totalidad el oficio No **10870** de fecha 26 de noviembre de 2004 y en su lugar efectuar un nuevo requerimiento en los siguientes terminos:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
03 DIC 2004
202063

P-586