



Industria y Comercio

SUPERINTENDENCIA

P. C. T.

Delegatura de propiedad Industrial

División de Nuevas Creaciones

03085892

SOLICITUD

PATENTE DE INVENCION

Entrada de fase nacional

21. EXPEDIENTE No. **03085892**

54. TÍTULO Inhibidores de Tirosina Cinasa
Novedosas.

51. CLASIFICACIÓN INTERNACIONAL A61K 31/416, C07D 401/14

71. SOLICITANTE Bristol-Myers Squibb Company

DOMICILIO Princeton, New Jersey, Estados Unidos de
América.

74. APODERADO Ramiro Castro Duque
202099.

22. BOGOTÁ, D. C., _____

PETITORIO

AS: 92.085

Industria y Comercio
SUPERINTENDENCIA



03 085892 00

SUPERINTENDENCIA Y CORRECCION
Radicacion : 03085892 00000000 Folios: 571
Fecha (A/B): 2003-09-25 17:05:43
Tramite : 011 PCT-PRTEY 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

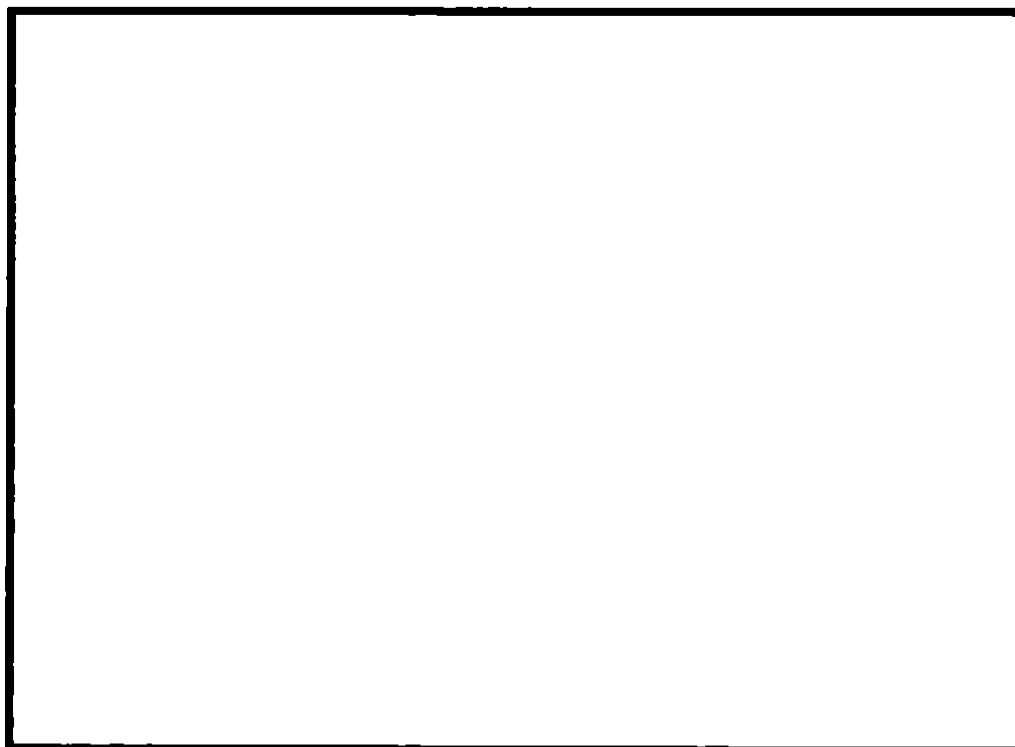
1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: BRISTOL - MYERS SQUIBB COMPANY Dirección: P.O. Box 4000, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail:		IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 18-58 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>170.322 TP 1003</u>
4 INVENTOR (ES) (72)	Nombre: Mark D. Wittman/Neelakantan Balasubramanian/Upender Velaparthi/Kurt Zimmermann/Mark G. Seuhler/Peiying Liu/Xiaopeng Sang/David B. Frennesson/Karen M. Stoffan/James G. Tarrant Dirección: 30 Fairlawn Dr., Wallingford, CT 06492, US; 26 Horsebarn Lane, Madison, CT 06443, US; 1298 Hartford Turnpike # 9J, North Haven, CT 06422, US; 5 Skeetfield Point Rd., Durham, CT 06422, US; 34 Ponsatt Rd., Higganum, CT 06441, US; 228 Devonshire Lane, Madison, CT 06443, US; 45 Hawthorne, Mead Dr. Glastonbury, CT 06033, US; 184 Conrad St., Naugatuck, CT 06770, US; 149 Whitney St., Hartford, CT 06105, US; 156 Handy Rd., Hamden, CT 06518, Estados Unidos de América (Respectiv.) Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)		
5 PCT (86)			
Solicitud Internacional No. <u>PCT/US02/09402</u>		Fecha <u>28-03-2002</u>	
Publicación Internacional No. <u>WO 02/079192 A1</u>		Fecha <u>10-10-2002</u>	
Título (54): <u>INHIBIDORES DE TIROSINA CINASA NOVEDOSOS</u>			
7 Clasificación Internacional (51) <u>C07D 401/14; A61K 31/416</u>			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	<u>US</u>	<u>28-03-2001</u>	<u>60/279,327</u>
9 Comprobante de pago No. <u>03-60.730</u> Fecha <u>25-09-2003</u>			

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$400.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Protocolo No. 19358
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

G.C. 170.322 de Bogotá T.P. 1093 del C.S.J.

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

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 60,730
FECHA : AGOSTO 27 DE 2003

3
SUPERINDUSTRIA Y COMERCIO
Radicacion : 03005092 00000000
Fecha (MM): 2003-09-26 17:05:43 Folios: 571
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

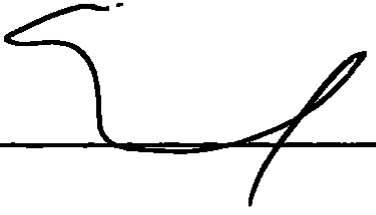
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	5732976	27/08/2003	23,740,000.00
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	5732977	27/08/2003	1,466,080.00

***** CONCEPTO *****

CANT. REENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRANITES DE SOL. DE PATENTE DE IN	400,000.00
	TOTAL :	\$ 400,000.00

SOM: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079192 A1

(51) International Patent Classification⁷: C07D 401/14,
A61K 31/4184

(US). TARRANT, James, G. [US/US]; 156 Handy Rd.,
Hamden, CT 06518 (US).

(21) International Application Number: PCT/US02/09402

(74) Agents: GIBBONS, Maureen et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(22) International Filing Date: 26 March 2002 (26.03.2002)

(25) Filing Language: English

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

(26) Publication Language: English

(30) Priority Data:
60/279,327 28 March 2001 (28.03.2001) US

(71) Applicant (*for all designated States except US*): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P. O. Box 4000, Route 206 and Princetown Road, Princeton, NJ 08543-4000 (US).

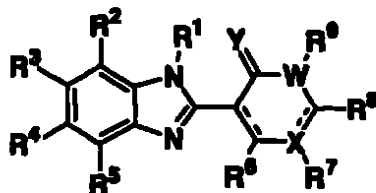
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,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

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): WITTMAN, Mark, D. [US/US]; 30 Fairlawn Dr., Wallingford, CT 06492 (US). BALASUBRAMANIAN, Neelakantan [US/US]; 26 Horsebarn Lane, Madison, CT 06443 (US). VELAPARTH, Upender [IN/US]; 1298 Hartford Turnpike #9J, North Haven, CT 06422 (US). ZIMMERMANN, Kurt [AT/US]; 5 Skansfield Point Rd., Durham, CT 06422 (US). SAULNIER, Mark, G. [US/US]; 34 Ponsell Rd., Higganum, CT 06441 (US). LIU, Pelying [CA/US]; 228 Devonshire Lane, Madison, CT 06443 (US). SANG, Xiaoping [CN/US]; 45 Hawthorne Mead Dr., Glastonbury, CT 06033 (US). FRENNESSON, David, B. [US/US]; 164 Conard St., Naugatuck, CT 06770 (US). STOFFAN, Karen, M. [US/US]; 149 Whitney St., Hartford, CT 06105

Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
— entirely in electronic form (except for this front page) and available upon request from the International Bureau

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

(54) Title: NOVEL TYROSINE KINASE INHIBITORS



(I)

(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof. The formula (I) compounds inhibit tyrosine kinase enzymes thereby making them useful as anti-cancer agents. The formula (I) compounds are also useful for the treatment of other diseases which can be treated by inhibiting tyrosine kinase enzymes.

NOVEL TYROSINE KINASE INHIBITORS

5 RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. Section 119(e) of U.S. Provisional Patent Application No. 60/279,327 filed March 28, 2001.

FIELD OF INVENTION

10 The present invention relates generally to the field of tyrosine kinase enzyme inhibition using novel small molecules.

BACKGROUND OF THE INVENTION

Tyrosine Kinases are a class of enzymes, which catalyze the transfer of the
15 terminal phosphate of adenosine triphosphate to the phenolic hydroxyl group of a tyrosine residue present in the target protein. Tyrosine kinases play a critical role in signal transduction for several cellular functions including cell proliferation, carcinogenesis, apoptosis, and cell differentiation (Plowman, G. D.; Ullrich, A.; Shawver, L. K.: Receptor Tyrosine Kinases As Targets For Drug Intervention.
20 *DN&P* (1994) 7: 334-339). Therefore inhibitors of these enzymes would be useful for the treatment or prevention of proliferative diseases which are dependent on these enzymes. Strong epidemiologic evidence suggests that the overexpression or activation of receptor protein tyrosine kinases leading to constitutive mitogenic signaling is an important factor in a growing number of human malignancies.
25 Tyrosine kinases that have been implicated in these processes include Abl, CDK's, EGF, EMT, FGF, FAK, Flk-1/KDR, HER-2, IGF-1R, IR, LCK, MET, PDGF, Src, and VEGF (Traxler, P.M. Protein Tyrosine Kinase Inhibitors in Cancer Treatment. *Exp. Opin. Ther. Patents* (1997) 7: 571-588; incorporated herein by reference). Hence, there is an ongoing need to investigate novel compounds that can be used to
30 regulate or inhibit tyrosine kinase enzymes.

SUMMARY OF THE INVENTION

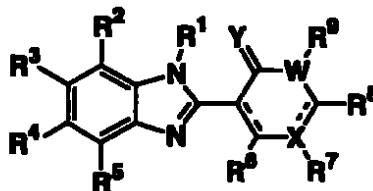
The present invention relates to compounds which inhibit tyrosine kinase enzymes, compositions which contain tyrosine kinase inhibiting compounds and

methods of using inhibitors of tyrosine kinase enzymes to treat diseases which are characterized by an overexpression or upregulation of tyrosine kinase activity such as cancer, diabetes, restenosis, arteriosclerosis, psoriasis, angiogenic diseases and immunologic disorders (Powis, G.; Workman, P. Signaling targets For The
 5 Development of Cancer Drugs. *Anti-Cancer Drug Design* (1994), 9: 263-277; Merenmies, J.; Parada, L. F.; Henkemeyer, M. Receptor Tyrosine Kinase Signaling in Vascular Development. *Cell Growth Differ* (1997) 8: 3-10; Shawver, L. K.; Lipsosn, K. E.; Fong, T. A. T.; McMahon, G.; Plowman, G. D.; Strawn, L. M. Receptor Tyrosine Kinases As Targets For Inhibition of Angiogenesis. *Drug*
 10 *Discovery Today* (1997) 2: 50-63; all herein incorporated by reference).

In addition to being used as single agents, it is contemplated that tyrosine kinase inhibitors can enhance the activity of cytotoxic or cytostatic treatments when used in combination with standard therapies known in the art.

The present invention is directed to compounds having formula I

15



I

20 its enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs and solvates thereof;

wherein

X is selected from the group consisting of N, C, C₁-C₃ alkyl, C₁-C₃ alkyl
 25 substituted with one or more R⁷, and a direct bond;

Y is selected from the group consisting of O and S ;

W is selected from the group consisting of N, C, O, and S, provided that when W is O or S, R⁹ is absent;

$R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9$ are each independently selected from the group consisting of H, C_{1-6} alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, OR^{60} , NO_2 , OH, SR^{60} , $NR^{60}R^{61}$, CN, CO_2R^{60} , $CONR^{60}R^{61}$, $CO_2NR^{60}R^{61}$, $NR^{62}CONR^{60}R^{61}$, $NR^{60}SO_2R^{61}$, $SO_2NR^{60}R^{61}$, $C(NR^{62})NR^{60}R^{61}$, aryl, heteroaryl,
 5 $(CH_2)_nOR^{60}$, $(CH_2)_nNR^{60}R^{61}$, $(CH_2)_nSR^{60}$, $(CH_2)_n$ aryl, $(CH_2)_n$ heteroaryl,
 $(CH_2)_n$ heterocycloalkyl, NH-Z-aryl, and NH-Z-heteroaryl;
 wherein n is 1 to 3; and

Z is selected from the group consisting of $C_1 - C_4$ alkyl, alkenyl, and alkynyl chain; Z having one or more hydroxy, thiol, alkoxy, thioalkoxy, amino, halo,
 10 $NR^{60}SO_2R^{61}$ groups; Z optionally incorporating one or more groups selected from the group consisting of CO, CNOH, $CNOR^{60}$, $CNNR^{60}$, $CNNCOR^{60}$ and $CNNSO_2R^{60}$;
 and

R^{60}, R^{61} , and R^{62} are independently selected from the group consisting of H,
 alkyl,
 15 alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, heteroaryl,
 heteroarylalkyl, and alkyl- R^{25} wherein

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino,
 alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, -
 $NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or
 20 heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

In preferred embodiments, R^1, R^7, R^8 and R^9 are H;

R^2 and R^4 are H or F;

Y is O;

25 X is selected from the group consisting of N and CH;

W is N;

R^3 is selected from the group consisting of H, methyl, ethyl, isopropyl,
 secondary butyl, cyclopropyl, F, and CF_3 ;

R^6 is selected from the group consisting of H, 2-aminomethylpyridine,
 30 $NHCH(CH_2OH)CH_2Ph$, $NHCH_2CH(OH)aryl$, and $NHCH(CH_2OH)CH_2aryl$; and

R^3 is selected from the group consisting of OR^{60} , $C(NH)NHR^{60}$, $C(O)NHR^{60}$ imidazole, imidazoline, tetrahydropyrimidine, piperazine, morpholine, homomorpholine, piperidine, pyrrolidine, homopiperazine and amino; wherein

R^{60} is selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, and alkyl- R^{25} wherein R^{25} is hydrogen, alkenyl, hydroxy, thiol, thioalkoxy, alkoxy, thioalkoxy, halo, cyano, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, or a heteroaryl or heterocycloalkyl; and R_{30} and R_{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

The invention also provides a pharmaceutical composition comprising a compound of formula I, as defined above, and a pharmaceutically acceptable carrier.

The invention further provides a pharmaceutical composition comprising a compound of formula I, as defined above, in combination with pharmaceutically acceptable carrier and at least one other anti-cancer agent optionally formulated as a fixed dose.

Additionally provided is a method of treating a condition associated with at least one tyrosine kinase enzyme comprising administering to a mammalian species in need of such treatment an effective amount of a compound of formula I, as defined above. Furthermore, the invention provides a method of treating a condition associated with at least one tyrosine kinase enzyme comprising administering to a mammalian species at least one other anti-cancer agent in combination with a compound of formula I, as defined above.

DESCRIPTION

The present invention provides for compounds of formula I, as defined above, pharmaceutical compositions employing such compounds and methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The term "alkyl" herein alone or as part of another group refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12 carbon atoms unless otherwise defined. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. When substituted, alkyl groups may be substituted with up to four substituent groups, R as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group". Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. Exemplary substituents may include but are not limited to one or more of the following groups: hydroxy, halo (such as F, Cl, Br, I), haloalkyl (such as CCl₃ or CF₃), alkoxy, alkylthio, cyano, carboxy (-COOH), alkylcarbonyl (-C(O)R), alkoxycarbonyl (-OCOR), amino, carbamoyl (-NHCOOR or -OCONHR), urea (-NHCONHR), thiol, (-SH), sulfoxy, sulfonyl, aryl, heteroaryl, and heterocycloalkyl. Alkyl groups as defined may also comprise one or more carbon to carbon double bonds or one or more carbon to carbon triple bonds. Alkyl groups may also be represented by the formula alkyl-R²⁵. In preferred embodiments, the alkyl group is a methyl, ethyl, propyl or butyl group and include substituted methyl, ethyl, propyl or butyl groups.

The term "alkenyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon double bond. An alkenyl group may be optionally substituted in the same manner as described for an alkyl group.

The term "alkynyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. An alkynyl group may be optionally substituted in the same manner as described for an alkyl group.

The term "alkoxy" as used alone or in combination herein refers to a straight or branched chain alkyl group covalently bonded to the parent molecule through an oxygen atom linkage containing from one to ten carbon atoms and the terms "C₁₋₆ alkoxy" and "lower alkoxy" refer to such groups containing from one to six carbon atoms, examples include, but are not limited to, methoxy, ethoxy, propoxy,

isopropoxy, butoxy, t-butoxy and the like. The term "optionally substituted" when used in connection with an alkoxy substituent refers to the replacement of up to two hydrogens, preferably on different carbon atoms with a radical selected from the group of lower alkyl, phenyl, cyano, halo, trifluoromethyl, nitro, hydroxy, alkanoyl, amino, monoalkyl amino and dialkylamino. Alkoxy groups may be substituted in the same manner that alkyl groups can be substituted as described above.

The term "sulfoxy" herein alone or as part of a group refers to $-SO$ and may be substituted with, for example, alkyl or aryl groups.

The term "sulfonyl" herein alone or as part of a group refers to $-SO_2$ and may be substituted with alkyl or aryl groups.

The term "amino" herein alone or as part of another group refers to $-NH_2$. An "amino" may optionally be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, alkenyl, alkynyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. Preferred substituents include alkylamino and dialkylamino, such as methylamino, ethylamino, dimethylamino, and diethylamino. These substituents may be further substituted with a carboxylic acid or any of the alkyl or aryl substituents set out herein. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiomorpholinyl, 4-sulfoxymorpholine, 4-sulfonylmorpholine, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-homopiperazinyl, 4-alkyl-1-homopiperazinyl, 4-arylalkyl-1-homopiperazinyl, 4-diarylalkyl-1-homopiperazinyl; 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

The term "aryl" herein alone or as part of another group refers to monocyclic or bicyclic aromatic rings, e.g. phenyl, substituted phenyl and the like, as well as groups which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, alkyl,

alkenyl, alkynyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, alkylaminocarbonyl, nitro, trifluoromethyl, amino, cycloalkyl, cyano, alkyl S(O)_m (m=O, 1, 2), or thiol. Aryl groups may also be substituted with heterocycloalkyl and heterocycloaryl groups to form fused rings, such as dihydrobenzofuranyl, oxindolyl, indolyl, indoliny, oxindolyl, benzoxazolidinonyl, benzoxazoliny and benzoxazolidinone.

The term "cycloalkyl" herein alone or as part of another group refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. Further, a cycloalkyl may be substituted. A substituted cycloalkyl refers to such rings having one, two, or three substituents, preferably one, selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, oxo (=O), hydroxy, alkoxy, thioalkyl, -CO₂H, -OC(=O)H, CO₂-alkyl, -OC(=O)alkyl, =N-OH, =N-O-alkyl, aryl, heteroaryl, heterocyclo, a five or six membered ketal (*i.e.* 1,3-dioxolane or 1,3-dioxane), -NR'R'', -C(=O)NR'R'', -OC(=O)NR'R'', -NR'CO₂'R'', -NR'C(=O)R'', -SO₂NR'R'', and -NR'SO₂'R'', wherein each of R' and R'' is independently selected from hydrogen, alkyl, substituted alkyl, and cycloalkyl, or R' and R'' together form a heterocyclo or heteroaryl ring. Cycloalkyl groups may also be substituted with hetero atoms such as O, N, and S to form heterocycloalkyl groups. Preferred heterocycloalkyl groups include optionally substituted morpholine, homomorpholine (7 membered ring), thiomorpholine, piperazine, homopiperazine (7 membered ring), and piperidine.

The term "heteroaryl" herein alone or as part of another group refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least

one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, hydroxy, alkoxy, thioalkyl, $-\text{CO}_2\text{H}$, $-\text{OC}(=\text{O})\text{H}$, $-\text{CO}_2$ -alkyl, $-\text{OC}(=\text{O})\text{alkyl}$, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, cycloalkyl, substituted cycloalkyl, heterocyclo, heteroaryl, $-\text{NR}'\text{R}''$, $-\text{C}(=\text{O})\text{NR}'\text{R}''$, $-\text{OC}(=\text{O})\text{NR}'\text{R}''$, $-\text{NR}'\text{CO}_2'\text{R}''$, $-\text{NR}'\text{C}(=\text{O})\text{R}''$, $-\text{SO}_2\text{NR}'\text{R}''$, and $-\text{NR}'\text{SO}_2\text{R}''$, wherein each of R' and R'' is independently selected from hydrogen, alkyl, substituted alkyl, and cycloalkyl, or R' and R'' together form a heterocyclo or heteroaryl ring.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrrolidinyl, imidazoliny, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, and the like.

Exemplary bicyclic heteroaryl groups include indolyl, indolinyl, oxindolyl, benzoxazolidinone, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indoliziny, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "halogen" or "halo" herein alone or as part of another group refers to chlorine, bromine, fluorine or iodine selected on an independent basis.

The term "hydroxy" herein alone or as part of another group refers to $-\text{OH}$.

The term "thioalkoxy" herein alone or as part of another group refers to an alkyl group as defined herein attached to the parent molecular group through a sulfur atom. Examples of thioalkoxy include, but are not limited to, thiomethoxy, thioethoxy, and the like.

Abbreviations: "Ph" represents phenyl; "Me" represents methyl; and "Et" represents ethyl.

An "anti-cancer agent" as used herein includes known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as
5 CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; anti-metabolites, such as methotrexate; tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; Her1/2 inhibitors and monoclonal antibodies directed
10 against growth factor receptors such as erbitux (EGF) and herceptin (Her2).

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with
15 reference to standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

When C₁₋₆ alkyl, alkenyl, alkynyl, cycloalkyl are substituted, they are preferably substituted with one or more hydroxy, cyano, carbamoyl, hydroxy, alkoxy, thiol, alkenyl, thioalkoxy, amino, alkylamino, amido, sulfonyl, sulfoxy, sulfonamido,
20 halo, heterocycloalkyl, aryl or heteroaryl.

When aryl or heteroaryl are substituted, they are preferably substituted with one or more alkyl, alkenyl, alkynyl, cyano, carbamoyl, hydroxy, alkoxy, thioalkoxy, amino, amido, sulfonamido, halo or with R', R'' wherein R', R'' form a ring that is fused to the aryl group. When CH₂aryl or heteroaryl are substituted, they are
25 preferably substituted with one or more alkyl, alkyenyl, alkynyl, cyano, carbamoyl, hydroxy, alkoxy, thioalkoxy, amino, amido, sulfonamido, or halogen.

When NH-Z-aryl or NH-Z-heteroaryl groups are substituted, they are preferably substituted with one or more alkyl, alkenyl, alkynyl, hydroxy, alkoxy, thioalkoxy, amino, halogen, nitro, nitrile, carboxylate, alkoxycarbonyl, carbamoyl,
30 ester, amide, aryl, or heteroaryl

The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C₁₋₆ alkyl" means a

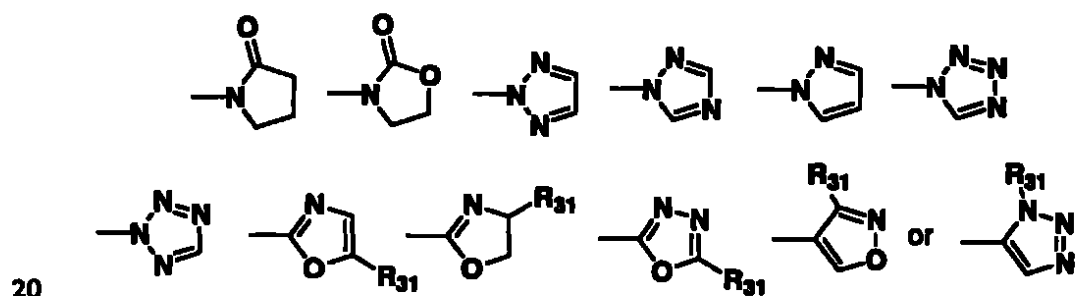
straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. Depending on the context, "C₁₋₆ alkyl" can also refer to C₁₋₆ alkylene which bridges two groups; examples include

5 propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C₂₋₆ alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. Depending on the context, "C₂₋₆ alkenyl" can also refer to C₂₋₆ alkenediyl which bridges two groups; examples

10 include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-diyl, 2-hexene-1,6-diyl, etc. "C₂₋₆ alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

The term "alkyl-R²⁵" includes optionally substituted alkyl groups such as

15 methyl, ethyl, propyl, and butyl, attached to an R²⁵ group. R²⁵ generally includes hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, -NHCOOH, -NHC(O)-, -NHSO₂-, -C(O)NH₂, heteroaryl or heterocycloalkyl groups such as morpholinyl or group having the formula:

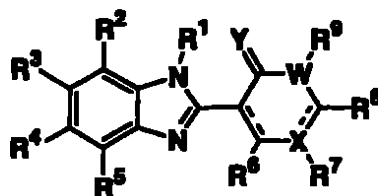


The terms "imidazole" and "imidazoline" herein alone or as part of another group includes substituted imidazoles and substituted imidazolines. Similarly, the term "tetrahydropyrimidine" includes substituted tetrahydropyrimidines. Likewise,

25 the terms "piperazine", "piperidine", "morpholines", "homopiperazines", "homomorpholines" and "pyrrolidine" include substituted piperazines, substituted

piperidines, substituted morpholines, substituted homomorpholines and substituted pyrrolidines, respectively.

Compounds of the present invention have the general formula I:



I

its enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs and solvates thereof;

10 wherein

X is selected from the group consisting of N, C, C₁-C₃ alkyl, C₁-C₃ alkyl substituted with one or more R⁷, and a direct bond;

Y is selected from the group consisting of O and S ;

15 W is selected from the group consisting of N, C, O, and S, provided that when W is O or S, R⁹ is absent;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ are each independently selected from the group consisting of H, C₁₋₆ alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, OR⁶⁰, NO₂, OH, SR⁶⁰, NR⁶⁰R⁶¹, CN, CO₂R⁶⁰, CONR⁶⁰R⁶¹, CO₂NR⁶⁰R⁶¹, NR⁶²CONR⁶⁰R⁶¹, NR⁶⁰SO₂R⁶¹, SO₂NR⁶⁰R⁶¹, C(NR⁶²)NR⁶⁰R⁶¹, aryl, heteroaryl, (CH₂)_nOR⁶⁰, (CH₂)_nNR⁶⁰R⁶¹, (CH₂)_nSR⁶⁰, (CH₂)_n aryl, (CH₂)_n heteroaryl, , (CH₂)_n heterocycloalkyl, NH-Z-aryl, and NH-Z-heteroaryl;

wherein n is 1 to 3; and

25 Z is selected from the group consisting of C₁ - C₄ alkyl, alkenyl, and alkynyl chain; Z having one or more hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, NR⁶⁰SO₂R⁶¹ groups; Z optionally incorporating one or more groups selected from the group consisting of CO, CNOH, CNOR⁶⁰, CNNR⁶⁰, CNNCOR⁶⁰ and CNNSO₂R⁶⁰; and

R⁶⁰, and R⁶¹ are independently selected from the group consisting of H, alkyl,

alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, heteroaryl, heteroarylalkyl, and alkyl- R^{25} wherein

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, -
 5 $NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

In some embodiments of the present invention, R^3 is $-OR^{60}$. R^{60} is alkyl, or -
 alkyl- R^{25} , wherein R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy,
 10 amino, halo, cyano, alkylsulfoxy, alkylsulfonyl, $-R^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} . In preferred embodiments, R^{60} is methyl, $-(CH_2)_nCH_2OH$, or $-(CH_2)_nCH_2N(CH_2CH_2)_2O$, and n is 0, 1, or 2.

In some embodiments, R^3 is piperazine, homopiperazine, 3-methylpiperazine,
 15 or 3,5-dimethylpiperazine being optionally substituted at the 4-N position with a compound selected from the group consisting of alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, alkyl- R^{25} , $-C(O)-R^{15}$, or $-CO_2R^{15}$ wherein R^{15} is hydrogen, alkyl, aryl, alkyl- R^{25} , amino or aryl; and R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, cyano, halo, sulfoxy, sulfonyl, arylsulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$,
 20 heteroaryl or heterocycloalkyl and R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} . In preferred embodiments, piperazine is substituted with Me, CH_2 cyclopropyl, $CH_2CH_2NMe_2$, $CH_2CH_2NEt_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe , CH_2CH_2NHEt , $N-CH_2CH_2N(CH_2CH_2)_2O$, $(CH_2)_nCH_2-R^{25}$ wherein R^{25} is OH, OMe, F, CN, CF_3 , $SOCH_3$ or SO_2CH_3 , wherein n is 0, 1, or 2.
 25

In some embodiments, R^3 is an amino group. Preferred amino groups include $NHCH_2CH_2OH$, $NMeCH_2CH_2OH$, $NEtCH_2CH_2OH$, $NHCH_2CH_2NH_2$, $NMeCH_2CH_2NH_2$, $NEtCH_2CH_2NH_2$, $NHCH_2CH_2NMe_2$, $NMeCH_2CH_2NMe_2$, $NEtCH_2CH_2NMe_2$, $NHCH_2CH_2NEt_2$, $NMeCH_2CH_2NEt_2$, $NEtCH_2CH_2NEt_2$,
 30 $NHCH_2CH_2N(CH_2CH_2)_2O$, $NMeCH_2CH_2N(CH_2CH_2)_2O$, $NEtCH_2CH_2N(CH_2CH_2)_2O$.

In some embodiments, R^3 is an optionally substituted piperidine. Preferred substituents are selected from the group consisting of hydroxy, thiol, amino,

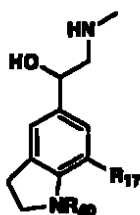
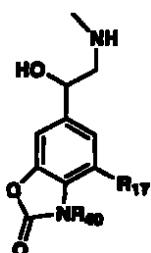
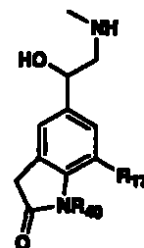
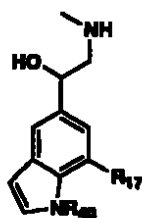
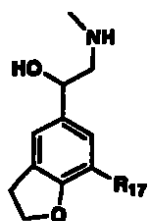
alkylamino, dialkylamino, alkoxy, thioalkoxy, 1,3 dioxolane $(-\text{OCHR}^{15})_2$, 1,3 dioxane $(-\text{OCHR}^{15}\text{CHR}^{15}\text{CHR}^{15}\text{O}-)$, $-\text{NHC}(\text{O})\text{R}^{15}$, $-\text{NHCO}_2\text{R}^{15}$, wherein R^{15} is hydrogen, alkyl or alkyl- R^{25} wherein R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, cyano, alkylsulfoxy, alkylsulfonyl, $-\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}\text{C}(\text{O})\text{R}^{31}$,
 5 $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $-\text{C}(\text{O})\text{NR}^{30}\text{R}^{31}$, heteroaryl or heterocycloalkyl; and R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

In some embodiments R^3 is an optionally substituted morpholine, homomorpholine, thiomorpholine, sulfoxymorpholine, or sulfonylmorpholine. Preferred substituents include hydroxy, thiol, amino, alkylamino, dialkylamino,
 10 alkoxy, thioalkoxy, alkyl- R^{25} , $-\text{NHC}(\text{O})\text{R}^{15}$, $-\text{NHCO}_2\text{R}^{15}$, wherein R^{15} is hydrogen, alkyl or alkyl- R^{25} wherein R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, cyano, alkylsulfoxy, alkylsulfonyl, $-\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}\text{C}(\text{O})\text{R}^{31}$, $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $-\text{C}(\text{O})\text{NR}^{30}\text{R}^{31}$, heteroaryl or heterocycloalkyl; and R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

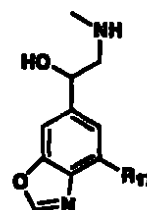
15 In some embodiments, R^3 is a pyrrolidine. Preferred pyrrolidines include, 3-hydroxyl pyrrolidine, 3- alkoxy pyrrolidine, and 3-alkylamino pyrrolidine.

According to one embodiment of the present invention, R^3 is an optionally substituted N-tetrahydropyrimidine or N-imidazoline wherein the substituents are, preferably, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanoalkyl, carboxyl, or
 20 carboxamide.

In some embodiments, R^6 is selected from the group consisting of H, 2-aminomethylpyridine, $\text{NHCH}_2\text{CH}(\text{OH})\text{aryl}$, and $\text{NHCH}(\text{CH}_2\text{OH})\text{CH}_2\text{aryl}$, wherein the aryl group is optionally substituted. In preferred embodiments, the aryl group is substituted with Br, Cl, F, or methoxy. In some embodiments, R^6 has one of the
 25 following formulae:



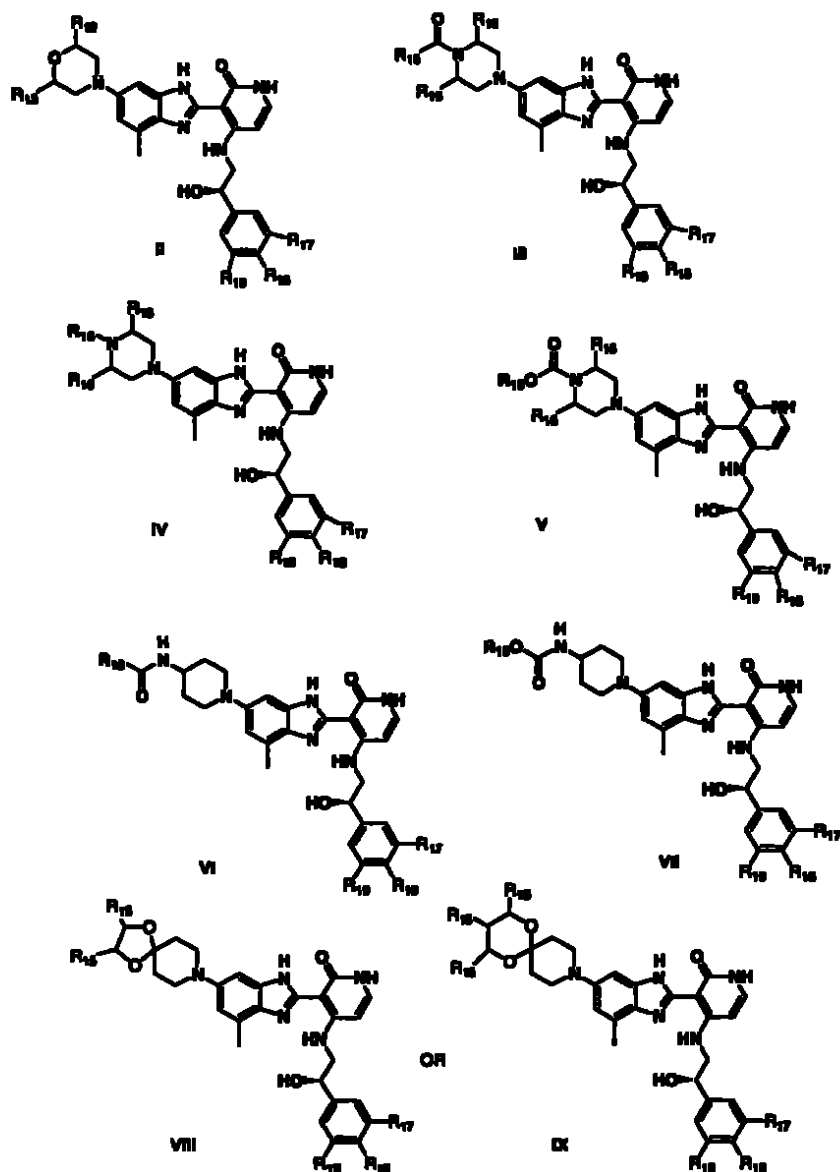
OR



wherein R^{40} is hydrogen or alkyl, preferably methyl, and R^{17} is hydrogen or halogen, such as Br, Cl or F.

5

Preferred compounds of the present invention have one of the following formulae:



wherein

- 5 R^{12} and R^{13} are, independently, hydrogen, alkyl, or alkyl- R^{25} ;
 R^{15} is hydrogen, alkyl, or alkyl- R^{25} ;
 R^{16} is independently, hydrogen or methyl;
 R^{17} , R^{18} and R^{19} are, independently, hydrogen, halogen, or alkoxy, or R^{18} and R^{19} together form a heterocycloalkyl or heteroaryl group;
10 R^{25} is hydrogen, hydroxy, thiol, alkenyl, alkoxy, thioalkoxy, amino, halo, cyano, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and
 R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl or alkyl- R^{25} .

In preferred embodiments, R¹² is hydrogen, methyl, hydroxymethyl, methoxymethyl, CH₂F, CH₂CN, CO₂H, or -CONR³⁰R³¹ wherein R³⁰ and R³¹ are, independently, hydrogen, or alkyl-R²⁵;

R¹³ is H;

5 R¹⁷ is Br, Cl or F;

R¹⁸ is halo or methoxy; and

R¹⁹ is H.

Suitable examples of salts of the compounds according to the invention include inorganic or organic acids. These include, but are not limited to, hydrochloride, hydrobromide, sulfate, methanesulfonate, maleate, fumarate, phosphate and other pharmaceutically acceptable salts. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of formula I or their pharmaceutically acceptable salts, are also included.

15 All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the compounds according to the invention embraces all possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

25 It should be understood that the present invention includes prodrug forms of the compounds of formula I. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

(a) Design of Prodrugs, edited by H. Bundgaard (Elsevier, 1985); and Methods in Enzymology, Vol. 42, pp. 309-396, edited by K.

30 Widder et al., (Academic Press, 1985);

(b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and

Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991);

(c) H. Bundgaard, Advanced Drug Deliver Reviews, 8, pp. 1-38 (1992);

(d) H. Bundgaard et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

(e) N. Kayeka et al., Chem. Phar. Bull., 32, 692 (1984).

5 The invention also provides a pharmaceutical composition comprising a compound of formula I, as defined above, and a pharmaceutically acceptable carrier and at least one other anti-cancer agent formulated as a fixed dose. Preferred anti-cancer agents are selected from the group consisting of: tamoxifen, toremifen, raloxifene, droloxifene, iodoxifene, megestrol acetate, anastrozole, letrozole, 10 borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, goserelin acetate, luprolide, finasteride, herceptin, methotrexate, 5-fluorouracil, cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotephan, vincristine, taxol, 15 taxotere, etoposide, teniposide, amsacrine, irinotecan, topotecan, an epothilone; a tyrosine kinase inhibitor such as Iressa or OSI-774; an angiogenesis inhibitor; an EGF inhibitor; a VEGF inhibitor; a CDK inhibitor; a Her1/2 inhibitor and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2).

20 The invention further provides a method of treating a condition via modulation of at least one tyrosine kinase enzyme comprising administering to a mammalian species in need of such treatment an effective amount of a compound of formula I, as defined above.

25 Additionally, the invention provides a method of treating a condition via modulation of at least one tyrosine kinase enzyme comprising administering to a mammalian species in need of such treatment an effective amount of a compound of formula I, as defined above, in combination (simultaneously or sequentially) with at least one other anti-cancer agent.

30 A preferred condition, treated by said methods of the instant invention, is cancer. Additionally, the tyrosine kinase enzyme may include (but is not limited to): Abl, CDK's, EGF, EMT, FGF, FAK, Flk-1/KDR, HER-2, IGF-1R, IR, LCK, MET, PDGF, Src, and VEGF.

The invention also provides a method for treating cancer, comprising administering to a mammalian species in need of such treatment, a therapeutically effective amount of at least one of the pharmaceutical compositions defined above.

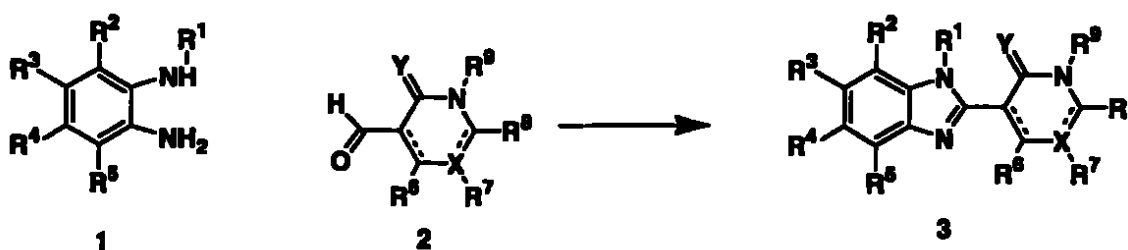
5 The invention further provides a method for treating proliferative diseases, comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of at least one of the pharmaceutical compositions defined above.

Certain compounds of formula I may generally be prepared according to the following schemes and the knowledge of one skilled in the art. Solvates (e.g., hydrates) of the compounds of formula I are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified by the following schemes below.

15 More specifically, Schemes I-VII illustrate the preparation of compounds claimed in this invention. The examples, which follow, illustrate the compounds that can be synthesized by these schemes. The schemes are not limited by the examples listed or by any substituents employed for illustrative purposes.

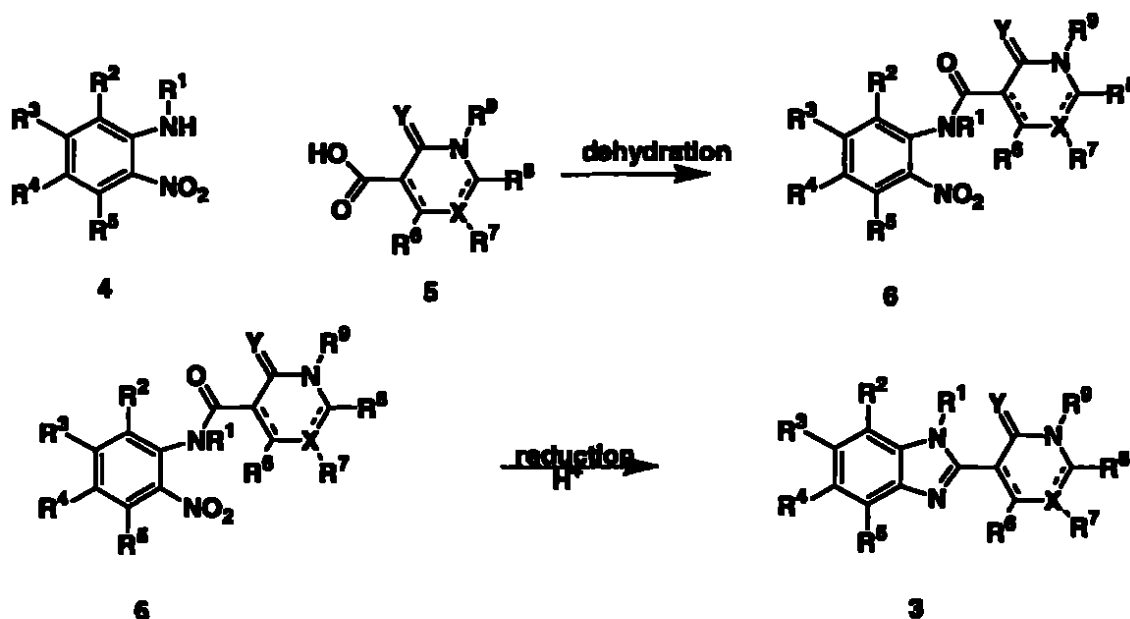
Scheme I describes the preparation of the benzimidazoles. The starting diamines **1** are readily available using literature methods or are obtained commercially. The diamine is then condensed with an aldehyde **2** to provide the benzimidazole **3**. Further modification of the functional groups on the aryl group of the benzimidazole or heterocycle of **3** are then envisioned.

25 Scheme I.



Alternatively, the benzimidazole could be formed in a step-wise manner (see Scheme II) by amide formation using the acid chloride of 5 or any of the commonly used peptide coupling reagents such as DCC (dicyclohexylcarbodiimide), EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), etc. Once the amide 6 was formed the nitro group could be reduced using catalytic hydrogenation, transfer hydrogenation or chemical reduction such as SnCl_2 or iron powder or other methods known in the art for reduction of aryl nitro groups. Treatment of the aniline with acid would then form the benzimidazole.

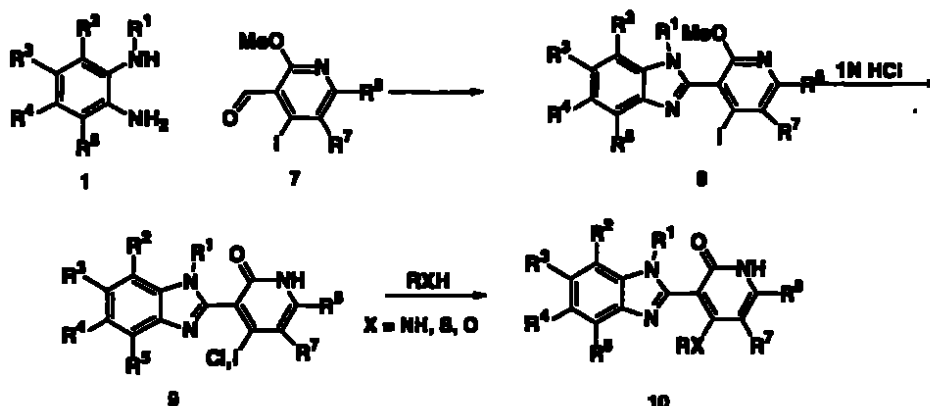
10 Scheme II.



For example, Scheme III illustrates the use of 4-iodo-2-methoxy-pyridine-3-carbaldehyde 7 to provide the functionalized benzimidazole 8. Hydrolysis of the methoxy group using protic acid conditions, TMSI (trimethylsilyl iodide), BBR_3 , or other conditions known in the art for cleaving a methyl ether would provide the halopyridone 9. Addition of heteroatom nucleophiles using amines, alcohols or thiols would then provide the substituted pyridones 10. Other functionality could be incorporated into the aldehyde and the above example is included for illustrative purposes only.

2/14

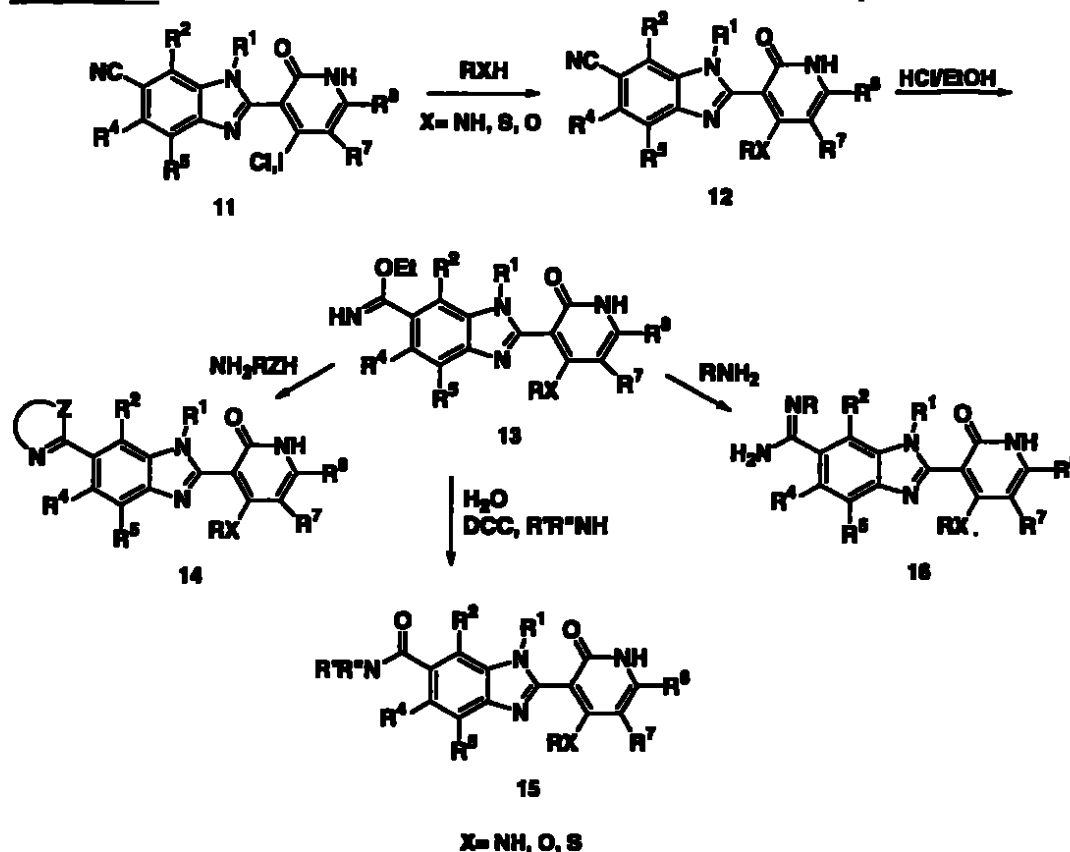
Scheme III



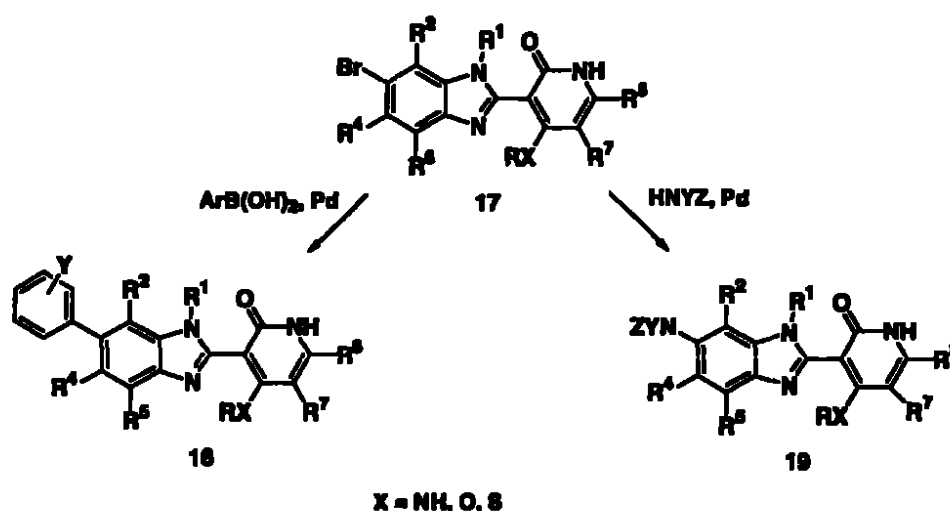
Likewise the aryl ring of the benzimidazole prepared using Schemes I or II

- 5 can be modified. For example introduction of a cyano group for R^3 on the benzimidazole allows for the formation of heterocycles such as imidazole, imidazolines, oxazolines, thiazolines, amides, or amidines. Scheme IV illustrates such transformations. Starting from the cyano-substituted benzimidazole 11 the heterocycle can be modified as illustrated in Scheme IV to provide 12. Imidate
- 10 formation preferably using ethanol and acid provides intermediate 13. Imidate 13 can be transformed using diamines to form imidazolines, amino alcohols to form oxazolines, amino acetals to form imidazoles, and amino thiols to form thiazolines 14. Alternatively the imidate can be hydrolyzed to the acid and coupled with amines using any of the standard amide formation reagents (DCC, EDCl, etc.) to form amides
- 15 15. Imidate 13 is also a useful intermediate for the preparation of amidines 16 by reacting with amines.

Scheme IV



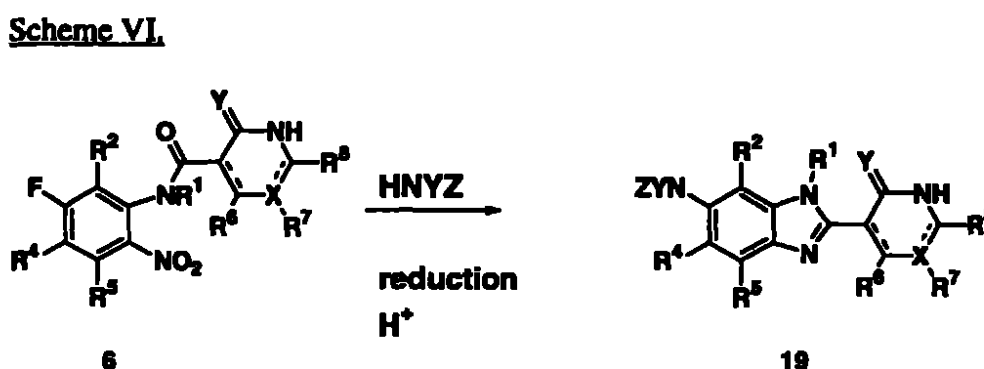
Scheme V illustrates further transformation of benzimidazoles that bear a halogen atom using palladium catalysis using conditions developed by Suzuki [Yang et al. *Acta Chem. Scand.* (1993) 221; Suzuki et al. *Synth. Commun.* (1981) 11: 513] or Buchwald/Hartwig [Buchwald et al. *J. Am. Chem. Soc.* (1994) 116: 7901; Hartwig et al. *J. Am. Chem. Soc.* (1994) 116: 5969; Hartwig. *Angew. Chem., Int. Ed. Engl.* (1998) 37: 2046] and variations of these methods. Preparation of a bromide substituted benzimidazole 17 could be envisioned to provide a substrate for Suzuki coupling with aryl, vinyl, and heterocyclic boronic acids to provide benzimidazoles 18. Likewise, amines and heterocycles such as piperazine or morpholine derivatives 19 can be prepared from the same bromide using amines under conditions described by Buchwald and Hartwig or variations thereof.

Scheme V

5

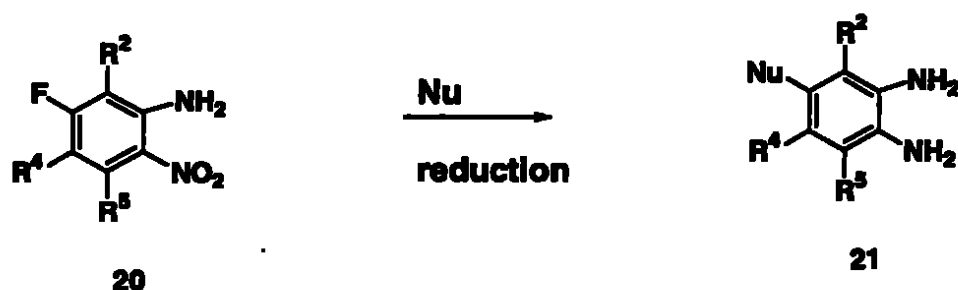
Alternatively amine and heterocyclic derivatives such as 19 can be prepared using intermediate 6 described in Scheme II. When the R³ of 6 is a halogen, preferably F, the halogen can be displaced with amines, alcohols, heterocyclic amines and other nitrogen containing heterocycles such as piperazine, piperidine, 4-amino piperidine, morpholine, imidazole, etc (Scheme VI). The terminal nitrogen of piperazine or 4-amino piperidine can then be alkylated using standard alkylation conditions or reacted with aldehydes in a reductive amination reaction to provide alkylated derivatives. Alternatively the terminal nitrogen atom of piperazine or 4-amino piperidine can be acylated or carbamoylated using any number of conditions that are routine for someone skilled in the art of organic synthesis. Following the example illustrated in Scheme II compounds such as 19 could be prepared.

20



Alternatively amines, heterocycles, and alcohols can be introduced at R₃ using a nucleophilic aromatic substitution reaction started from an intermediate 20 where R₃ is halogen, preferably F, the halogen can be displaced with amines, alcohols, heterocyclic amines and other nitrogen containing heterocycles such as piperazine, piperidine, 4-amino piperidine, morpholine, imidazole, etc (Scheme VII). The terminal nitrogen of piperazine or 4-amino piperidine can then be alkylated using standard alkylation conditions or reacted with aldehydes in a reductive amination reaction to provide alkylated derivatives. Alternatively the terminal nitrogen atom of piperazine or 4-amino piperidine can be acylated or carbamoylated using any number of conditions that are routine for someone skilled in the art of organic synthesis. The resulting nitro aniline could be reduced to the diamine 21 and processed as illustrated in Scheme III.

Scheme VII



Utility

20

The compounds according to the invention have pharmacological properties; in particular, the compounds of formula I are tyrosine kinase enzyme inhibitors. The novel compounds of formula I are thus useful in the therapy of a variety of proliferative diseases (including but not limited to diseases associated with tyrosine kinase enzymes) such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurodegenerative disorders and cardiovascular disease.

More specifically, the compounds of formula I are useful in the treatment of a variety of cancers, including, but not limited to, the following:

- a) carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder,

30

ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

5 b) hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

c) hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

10 d) tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

e) tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

15 f) other tumors, including sacroma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of tyrosine kinases in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may
20 be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic
25 shock, and fungal infections.

Compounds of formula I may induce apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of formula I, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned herein above), viral infections (including but not limited to
30 herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated

glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of formula I may modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of formula I may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of formula I may also be useful in inhibiting tumor angiogenesis and metastasis.

The compounds of this invention may also be useful in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate; tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; Her1/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2).

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent or treatment within its approved dosage range.

Compounds of formula I may also be administered sequentially with known

anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent(s).

Further subject matter of the invention also includes pharmaceuticals for use, as described above, including controlling cancer, inflammation and arthritis, which contain at least one compound of the formula I as defined above or at least one of its pharmacologically acceptable acid addition salts, and the use of a compound of the formula I as defined above for the preparation of a pharmaceutical having activity against proliferative diseases as described previously including against cancer, inflammation and/or arthritis.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts.

Biological Assays

A. CDK 2/cyclin E Kinase Assay

Kinase reactions consisted of 5 ng of baculovirus expressed GST-CDK2/cyclin E complex, 0.5 µg GST-RB fusion protein (amino acids 776-928 of retinoblastoma protein), 0.2 µCi ³³P γ-ATP, 25 µM ATP in 50 µl kinase buffer (50 mM Hepes, pH 8.0, 10 mM MgCl₂, 1 mM EGTA, 2 mM DTT). Reactions were incubated for 45 minutes at 30° C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15%. TCA precipitates were collected onto GF/C unfilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester (Packard Instrument Co., Meriden, CT) and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Dose response curves were generated to determine the

concentration required inhibiting 50% of kinase activity (IC_{50}). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at six concentrations, each in triplicate. The final concentration of DMSO in the assay equaled 2%. IC_{50} values were derived by non-linear regression analysis and have a
5 coefficient of variance ($SD/mean, n=6$) = 14%.

B. EMT Kinase Assay

A filter-based kinase assay, measuring the phosphorylation of Gst-SLP76 by
10 Gst-Emtk, was employed to determine the compound inhibitory activity against Emt. The kinase reaction was performed in a 96-well plate at room temperature for 15 min before being terminated by adding 100 μ l of 20% trichloroacetic acid (TCA) containing 0.1 M sodium pyrophosphate. The kinase reaction mixture (60 μ l) contained 25 mM HEPES, pH 7.0, 0.1 mg/ml BSA, 5 mM $MgCl_2$, 5 mM $MnCl_2$, 8 ng
15 of enzyme (Gst-Emtk), 5 μ g of the substrate protein (Gst-SLP76), 1 μ M ATP, 0.4 μ Ci of [γ - P^{33}]ATP and the tested compound (at various concentrations). After termination, the proteins were allowed to precipitate in the presence of TCA for 1 hr at 4 °C. The precipitated proteins were then harvested on a filter plate (UniFilter-96, GF/C, Packard Instrument) and washed to remove excess [γ - P^{33}]ATP. The
20 radioactivity was determined using a TopCount NXT (Packard Instrument) after adding 35 μ l of Microscint 20 (Packard Instrument).

C. FAK Tyrosine Kinase Assay

25 The Focal Adhesion kinase was assayed using the synthetic polymer poly(Glu/Tyr) (Sigma Chemicals) as a phosphoacceptor substrate. Each reaction mixture consisted of a total volume of 50 μ l and contained 100 ng of baculovirus-expressed enzyme, 2 μ g of poly(Glu/Tyr), 1 μ M of ATP, and 0.2 μ Ci of [γ - P^{33}]ATP. The mixtures also contained 40 mM Tris.HCl, pH 7.4, 1 mM $MnCl_2$, 0.5 mM DTT,
30 and 0.1 mg/ml bovine serum albumin. The reaction mixtures were incubated at 26°C for 1 hour and kinase activity was determined by quantitation of the amount of radioactive phosphate transferred to the poly(Glu/Tyr) substrate. Incorporation was measured by the addition of cold trichloroacetic acid (TCA) precipitation of the proteins which were collected onto GF/C unfilter plates (Packard Instrument Co.,

Meriden, CT) using a Filtermate universal harvester and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Compounds were dissolved in dimethyl sulfoxide to a concentration of 10 mM and were evaluated at six concentrations, each in triplicate. The final concentration of DMSO added to the kinase assays was 0.5%, which has been shown to have no effect on kinase activity. IC₅₀ values were derived non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

D. HER-1/HER-2 Kinase Assay

Kinase reactions consisted of 10 ng of baculovirus expressed GST- HER1, 100 ng of HER2, 100 ng/ml poly(Glu/Tyr) (Sigma), 0.2 μ Ci ³³P γ -ATP, 1 μ M ATP in 50 μ l kinase buffer (50 mM Tris, pH 7.5, 10 mM MnCl₂, 0.5 mM DTT). Reactions were incubated for 1h at 27 C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration 15%. TCA precipitates were collected onto GF/C unifilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester (Packard Instrument Co., Meriden, CT) and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Dose response curves were generated to determine the concentration required to inhibit 50% of kinase activity (IC₅₀). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at six concentrations, each in triplicate. The final concentration of DMSO in the assay equaled 1%. IC₅₀ values were derived by non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

E. IGF- Receptor Tyrosine Kinase Assay

The IGF-1 receptor tyrosine kinase was assayed using the synthetic polymer poly(Glu/Tyr) (Sigma Chemicals) as a phosphoacceptor substrate. Each reaction mixture consisted of a total volume of 50 μ l and contained 125 ng of baculovirus expressed enzyme, 2.5 μ g of poly(Glu/Tyr), 25 μ M of ATP, and 0.1 μ Ci of [γ -³³P]ATP. The mixtures also contained 20 mM MOPS, pH 7.0, 5 mM MnCl₂, 0.5 mM DDT, and 0.1mg/ml bovine serum albumin. The reaction mixtures were incubated at 30°C for 45 minutes and kinase activity was determined by quantitation of the amount

of radioactive phosphate transferred to the poly(Glu/Tyr) substrate. Incorporation was measured by the addition of cold trichloroacetic acid (TCA) precipitation of the proteins which were collected onto GF/C unfilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Compounds were dissolved in dimethyl sulfoxide to a concentration of 10 mM and were evaluated at six concentrations, each in triplicate. The final concentration of DMSO added to the kinase assays was 0.5%, which has been shown to have no effect on kinase activity. IC₅₀ values were derived by non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

F. Insulin Receptor Tyrosine Kinase Assay

The Insulin Receptor Tyrosine kinase was assayed using the synthetic polymer poly(Glu/Tyr) (Sigma Chemicals) as a phosphoacceptor substrate. Each reaction mixture consisted of a total volume of 50 μ l and contained 90 ng of baculovirus-expressed enzyme, 2.5 μ g of poly(Glu/Tyr), 25 μ M of ATP, and 0.1 μ Ci of [γ -³³P]ATP. The mixtures contained also 20 mM Tris.HCl, pH 7.4, 5 mM MnCl₂, 0.5 mM DTT, and 0.1 mg/ml bovine serum. The reaction mixtures were incubated at 26°C for 1 hour and kinase activity was determined by quantitation of the amount of radioactive phosphate transferred to the poly(Glu/Tyr) substrate. Incorporation was measured by the addition of cold trichloroacetic acid (TCA) precipitation of the proteins which were collected onto GF/C unfilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Compounds were dissolved in dimethyl sulfoxide to a concentration of 10 mM and were evaluated at six concentrations, each in triplicate. The final concentration of DMSO added to the kinase assays was 0.5%, which has been shown to have no effect on kinase activity. IC₅₀ values were derived non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

19

G. LCK Kinase Assay

Kinase reactions consisted of 10 ng of baculovirus expressed 10ng GST-Lck, 100 ng/ml poly(Glu/Tyr) (Sigma), 0.2 μ Ci 33P γ -ATP, 1 μ M ATP in 50 μ l kinase buffer (50 mM Tris, pH 7.5, 10 mM MnCl₂, 0.5 mM DTT). Reactions were incubated for 1h at 27 C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration 15%. TCA precipitates were collected onto GF/C unfilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester (Packard Instrument Co., Meriden, CT) and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Dose response curves were generated to determine the concentration required to inhibit 50% of kinase activity (IC₅₀). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at six concentrations, each in triplicate. The final concentration of DMSO in the assay equaled 1%. IC₅₀ values were derived by non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

H. MET Kinase Assay

Kinase reactions consisted of 10ng of baculovirus expressed GST-Met, 2.5ug poly(Glu/Tyr) (Sigma), 0.2 μ Ci 33P γ -ATP, 10 μ M ATP in 50 μ l kinase buffer (40mM Tris, pH 7.5, 1mM MnCl₂, 0.50 mM DTT). Reactions were incubated for 1h at 27 C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration 3.5%. TCA precipitates were collected onto GF/C unfilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester (Packard Instrument Co., Meriden, CT) and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Dose response curves were generated to determine the concentration required to inhibit 50% of kinase activity (IC₅₀). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at seven concentrations, each in triplicate. The final concentration of DMSO in the assay equaled 1%. IC₅₀ values were derived by non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

I. PDGF Receptor Kinase Assay

Kinase reactions consisted of 70ng of baculovirus expressed GST-PDGFbR, 0.3ug biotinylated poly(Glu/Tyr) (Sigma), in 50 µl kinase buffer (20 mM Hepes, pH 7.5, 0.7uM ATP, 10mM MnCl₂, 0.5mM DTT, 0.15mM NaCl, 0.1mg/ml BSA). Reactions were incubated for 30 minutes at room temperature with shaking and stopped by the addition of 10ul of 0.2M EDTA, pH8.0. 150ul of HTRF detection buffer was added and incubated for 1 hour and 30 minutes at room temperature. Counts were quantitated on Discovery HTRF Packard Instrument.

10

J. VEGFR-2 (KDR) Kinase Assay

Kinase reactions consisted of 7.5ng of baculovirus expressed GST-KDR, 1.5ug poly(Glu/Tyr) (Sigma), 0.04µCi 33P γ-ATP, 2.5 µM ATP in 50 µl kinase buffer (25 mM Tris, pH 7.5, 1.8 mM MnCl₂, 0.0.625 mM DTT). Reactions were incubated for 1h at 27 C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration 15%. TCA precipitates were collected onto GF/C unfilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester (Packard Instrument Co., Meriden, CT) and the filters were quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Dose response curves were generated to determine the concentration required to inhibit 50% of kinase activity (IC₅₀). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at six concentrations, each in triplicate. The final concentration of DMSO in the assay equaled 1%. IC₅₀ values were derived by non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

25

K. Cytotoxicity assay (HT-29-colon; Colo205, MCF-7-breast)

Tumor cell lines are maintained in McCoy's 5A medium (GIBCO) and 10% heat inactivated fetal bovine serum (GIBCO). The *in vitro* cytotoxicity is assessed in tumor cells by a tetrazolium-based colorimetric assay which takes advantage of the metabolic conversion of MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) (Promega) to a reduced form that absorbs light at 492 nm (1). Cells are seeded 24 hr prior to drug

35

addition. Following a 72 hour incubation at 37°C with serially diluted test compound, MTS (Riss, T.L, et al., Comparison of MTT, XTT, and a novel tetrazolium compound MTS for in vitro proliferation and chemosensitivity assays., *Mol. Biol. Cell* 3 (Suppl.):184a, 1992), in combination with the electron coupling agent phenazine

- 5 methosulfate, is added to the cells. The incubation is continued for 3 hours, then the absorbency of the medium at 492 nm is measured with a spectrophotometer to obtain the number of surviving cells relative to control populations. The results are expressed as median cytotoxic concentrations (IC₅₀ values).

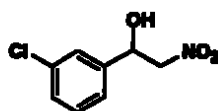
- 10 **Table 1 - Biological Activity (uM); all compounds in the table had kinase activity of <25uM against one or more of the following kinases CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF. HT-29 and Colo205 are human colon tumor cell lines, and MCF-7 is a human breast tumor cell line.**

15

Example	HT-29	MCF-7	Colo205
1	1.0		
3	2.0		
399	0.4		0.8
400	0.8		0.9
411	0.7		0.9
517	0.3		
519	0.3	0.6	
520	0.6	0.2	
521	0.5		
522	0.7	0.1	0.1
523	0.6		
524	0.6		
525	1.1		
526	1.4		
527	1.3	0.1	0.3
534	0.4		
538	0.9		
544	0.3	0.6	
553	0.9	0.3	0.2
554	0.7	0.2	0.3
555	0.2	0.1	0.2
559	0.6	0.3	
574	0.2		
581	0.2	0.3	
582	0.1	0.2	

583	0.1	0.2	
584	0.3	0.2	
585	0.7	0.3	
590	0.8	0.2	0.2
593	0.7		

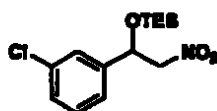
General Procedure for the Preparation of 2-Hydroxy-2-(substituted-phenyl)-ethylamines:



5

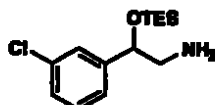
1-(3-Chloro-phenyl)-2-nitro-ethanol: To a solution of 3-chloro-benzaldehyde (20 g, 0.142 mol) in nitromethane (100 mL) were added magnesium sulfate (37.6 g, 0.312 mol) and phosphazene base P_1 -*t*-bu-tris(tetramethylene) (4.43 g, 0.014 mol). The reaction mixture was stirred at room temperature for 2 h. After concentration *in vacuo*, the residue was purified by flash chromatography (25% EtOAc / hexane) to yield the title compound (26.4 g, 100%) as a green-yellow oil. ^1H NMR (300 MHz, DMSO- d_6) δ 7.53 (1H, s), 7.35 – 7.42 (3H, m), 6.23 (1H, broad s), 5.32 – 5.33 (1H, m), 4.90 (1H, dd, J = 3.2, 12.4 Hz), 4.60 (1H, dd, J = 1.2, 12.4 Hz).

15



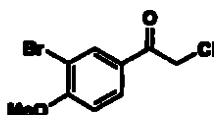
[1-(3-Chloro-phenyl)-2-nitro-ethoxy]-triethyl-silane: To a solution of 1-(3-chloro-phenyl)-2-nitro-ethanol (26 g, 0.14 mol) in DMF (50 mL) were added imidazole (28.6 g, 0.42 mol) and chlorotriethylsilane (25.3 g, 0.17 mol). The reaction mixture was stirred at room temperature for 2 h. After quenching with water, the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4 , and filtered. After removal of solvent, the crude product was purified by flash chromatography (2% EtOAc / hexane) to yield the title compound (37 g, 91%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.40 (1H, s), 7.27 – 7.32 (3H, m), 5.40 (1H, dd, J = 3.2, 9.5 Hz), 4.51 (1H, dd, J = 9.5, 12.1 Hz), 4.36 (1H, dd, J = 3.3, 12.1 Hz), 0.85 (9H, t, J = 7.5 Hz), 0.54 (6H, q, J = 7.5 Hz).

25



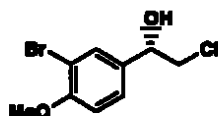
2-(3-Chloro-phenyl)-2-triethoxysilyloxy-ethylamine: Raney nickel (1 g) was washed with distilled water five times and methanol three times. [1-(3-Chloro-phenyl)-2-nitro-ethoxy]-triethyl-silane (10 g, 0.032 mol) and Raney nickel in methanol (100 mL) was hydrogenated (35 psi) at room temperature for 14 h. The reaction mixture was filtered through a pad of celite and rinsed with methanol. Concentration of the filtrate to dryness gave the title compound (5.6 g, 62%) as a colorless oil which was used for the next step without purification. ¹H NMR (300 MHz, CDCl₃) δ 7.32 (1H, s), 7.18-7.26 (3H, m), 4.70 (1H, t, *J* = 5.8 Hz), 2.86 (2H, m), 0.89 (9H, t, *J* = 7.9 Hz), 0.56 (6H, q, *J* = 7.8 Hz). LRMS (M+H)⁺ *m/z* 286.

General Procedure for the Preparation of 2-Hydroxy-2-(substituted-phenyl)-ethylamines:



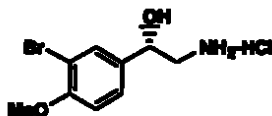
4-methoxy-3-bromophenyl chloroacetophenone: To a suspension of AlCl₃ (13.4g, 0.10 mol) in methylene chloride (40mL) was added a solution of 2-bromoanisole (12.5 mL, 0.10 mol) and chloroacetyl chloride (8 mL, 0.10 mol) at 0°C. The solution was warmed to ambient temperature for two hours and poured onto ice and extracted with methylene chloride, washed with saturated sodium bicarbonate solution, brine, and dried over MgSO₄. The solution was filtered, concentrated and crystallized from EtOH to give 15.37g of white solid. LRMS [M-H]⁻ 260.8; IR (KBr) 1697, 1048, 1255 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 8.18 (s, 1H), 7.94 (dd, *J* = 8.67 Hz, 1H), 6.96 (d, *J* = 8.67 Hz, 1H), 4.62 (s, 2H), 3.98 (s, 3H); ¹³C NMR (CDCl₃, 75.5 Hz) δ 188.8, 160.3, 134.1, 129.9, 128.2, 112.4, 111.3, 56.6, 45.3.

General Procedure for chiral reduction of chloroketones and ammonolysis :



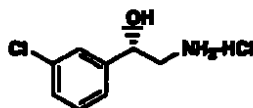
5 (S)-1-[4-methoxy-3-bromophenyl]-2-chloroethanol : To a solution of (S)-Methyl-CBS-oxazaborolidine (1M in toluene, 0.745 mL, 0.745 mmol) and BH₃-THF (8mL, 8 mmol) was added at the same time a solution of BH₃-THF (19mL, 19 mmol) and a solution of the chloroketone (10.03g, 37.98 mmol) in 19 mL of THF. Both solutions were added dropwise over 30 minutes. The solution was stirred for 1 hour and quenched with the slow addition of methanol (50mL). The solution was concentrated and the residue chromatographed over a short silica gel column (1:1 hexane/ethyl
 10 acetate) to give a quantitative yield (10.0g) of chlorohydrin as a clear oil. IR (KBr) 1053, 1258, 3406 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.59 (s, 1H), 7.30 (dd, J=2.16 Hz, 1H), 6.90 (d, J=8.46 Hz, 1H), 4.83 (dd, J= 3.57 Hz, 1H), 3.90 (s, 3H), 3.64 (ddd, J= 3.6, 11.1, 8.7, 2H), 2.04 (b s, 1H). ¹³C NMR (CDCl₃, 75.5 MHz) δ 155.9, 133.5, 131.1, 126.3, 111.9, 73.1, 60.4, 56.3, 50.7.

15



(S) 2-Amino-1-[3-chloro-4-methoxyphenyl]ethanol Hydrochloride : To a solution of the chlorohydrin (10.0g, 37.9 mmol) in 120 mL of methanol at -40°C was added
 20 100 grams of ammonia. The solution was sealed in a pressure bottle and warmed to ambient temperature and stirred for 48 hours. The solution was cooled and opened. The ammonia was allowed to evaporate and solution concentrated. The residue was crystalized from ethanol/ethyl acetate to give 3.83g of white solid (35%). The material was reacted with Boc₂O in ethyl acetate and saturated sodium bicarbonate
 25 and analyzed by chiral HPLC using a chiralcel OJ column using 95% hexane/ethanol as elutant and determined to by 98%ee. Additional crops were collected – 2.96g and 1.41g for a total of 75% yield. LRMS [M+H]⁺ 246; IR (cm⁻¹, KBr) 1055, 1261, 3001, 2948, 3356; ¹H NMR (500MHz, DMSO) δ 8.09 (b s, 2 H), 7.58 (s, 1H), 7.36 (dd, J=2.05, 6.45 Hz, 1H), 7.11 (d, J=8.5 Hz, 1H) 6.10 (s, 1H), 4.80 (m, 1H), 3.84 (s,

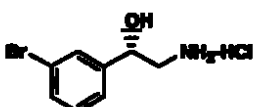
3H), 3.00 (ddd, $J = 2.7, 12.6, 9.5$ Hz, 2H); ^{13}C NMR (DMSO, 75.5 MHz) δ 154.8, 135.4, 130.4, 126.6, 112.4, 110.4, 67.9, 56.2, 45.4.



5

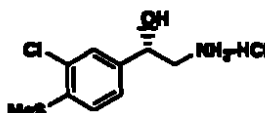
(S)-2-Amino-1-[3-chlorophenyl]ethanol Hydrochloride : was prepared according to the general procedure outlined above. LRMS $[M+H]^+$ 172; IR (KBr, cm^{-1}) 3048, 3351, 2952; ^1H NMR (300MHz, MeOD) δ 7.48 (s, 1H), 7.35 (m, 3H), 3.31 (ddd, $J = 1.5, 3.12, 9.15$ Hz 2H).

10

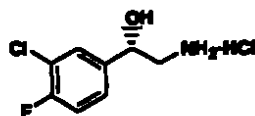


(S)-2-Amino-1-[3-bromophenyl]ethanol Hydrochloride : was prepared according to the general procedure outlined above. LRMS $[MH]^+$ 217.9; IR (KBr, cm^{-1}) 3025, 3443, 2891; ^1H NMR (500MHz, DMSO) δ 7.93 (b s, 2H), 7.60 (s, 1H), 7.52 (d, 1H), 7.41 (s, 1H), 7.35 (d, $J = 7.7$ Hz, 1H) 6.17 (s, 1H), 4.82 (m, 1H), 3.08 (ddd, $J = 2.6, 12.7, 9.6$ Hz, 2H); ^{13}C NMR (DMSO, 75.5 MHz) δ 144.4, 130.5, 128.7, 125.0, 121.6, 68.3, 45.1.

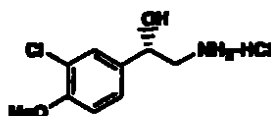
20



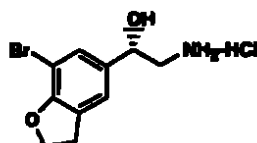
(S)-2-Amino-1-[3-chloro-4-methylthiophenyl]ethanol Hydrochloride : was prepared according to the general procedure outlined above. LRMS $[M+H]^+$ 217.9; IR (KBr, cm^{-1}) 3007, 3358; ^1H NMR (500MHz, DMSO) δ 8.12 (b s, 2H), 7.46 (s, 1H), 7.37 (s, 1H), 7.35 (d, 1H) 6.19 (d, 1H), 4.83 (m, 1H), 3.01 (ddd, $J = 3.2, 12.8, 9.3$ Hz, 2H); ^{13}C NMR (DMSO, 75.5 MHz) δ 139.6, 136.5, 129.8, 126.6, 125.4, 68.0, 45.2, 14.2.



(S)-2-Amino-1-[3-chloro-4-fluorophenyl]ethanol Hydrochloride : was prepared according to the general procedure outlined above. LRMS [M+H]⁺ 189.9; IR (KBr, cm⁻¹) 1509, 3008, 3359; ¹H NMR (500MHz, DMSO) δ 8.21 (b s, 2H), 7.61 (d, J=7.85 Hz, 1H), 7.42 (m, 2H), 6.29 (s, 1H), 4.88 (m, 1H), 3.03 (ddd, J= 3.4, 12.8, 9.2 Hz, 2H); ¹³C NMR (DMSO, 75.5 MHz) δ 157.5, 155.5, 139.7, 128.1, 126.7, 119.3, 116.7, 109.0, 67.8, 45.2.



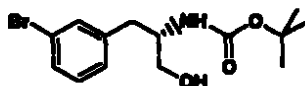
(S)-2-Amino-1-[3-chloro-4-methoxyphenyl]ethanol Hydrochloride : was prepared according to the general procedure outlined above. LRMS [M+H]⁺ 202; IR (KBr, cm⁻¹) 3354, 3003, 2949, 1288, 1064; ¹H NMR (500MHz, DMSO) δ 8.18 (brs, 3H), 7.43 (d, J=2.0Hz, 1H), 7.31 (dd, J=8.5, 2.0Hz, 1H), 7.14 (d, J=5.1Hz, 1H), 6.11 (s, 1H), 4.81 (m, 1H), 3.84 (s, 3H), 2.99 (dd, J=13, 3.5Hz, 1H), 2.83 (dd, J=12.5, 9Hz, 1H); ¹³C NMR (DMSO, 125MHz) δ 153.9, 135.0, 127.3, 125.8, 120.8, 112.6, 68.0, 56.1, 45.5; Elemental Analysis Calcd for C₉H₁₂ClNO₂·HCl: C, 45.39; H, 5.50; N, 5.88. Found: C, 45.38; H, 5.43; N, 5.70.



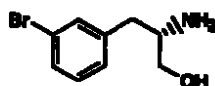
(S)-2-Amino-1-(7-bromo-2,3-dihydrobenzofuran-5-yl)-2-aminoethanol Hydrochloride : was prepared according to the general procedure outlined above. LRMS [M+H]⁺ 258; IR (KBr, cm⁻¹) 3349, 3006, 2928, 1485, 1045, 983; ¹H NMR (500MHz, DMSO) δ 8.13 (brs, 3H), 7.29 (s, 1H), 7.23 (s, 1H), 6.08 (d, J=4 Hz, 1H), 4.76 (m, 1H), 4.61 (t, J=9Hz, 2H), 3.29 (t, J=9Hz, 2H), 2.96 (dd, J=13, 3.5Hz, 1H),

2.82 (dd, $J=13,9.5\text{Hz}$, 1H); ^{13}C NMR (DMSO, 125MHz) δ 156.3, 135.9, 129.1, 128.1, 122.1, 100.9, 71.5, 68.2, 45.6, 29.9; Elemental Analysis Calcd for $\text{C}_{10}\text{H}_{12}\text{BrNO}_2\cdot\text{HCl}$: C, 40.77; H, 4.44; N, 4.75. Found: C, 40.77; H, 4.63; N, 4.63.

5 **General Procedure for the Preparation of 2-Amino-3-(substituted-phenyl)-propanol:**

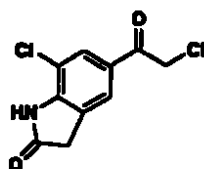


- 10 **(S)-[2-(3-Bromo-phenyl)-1-hydroxymethyl-ethyl]-carbamic acid *tert*-butyl ester:**
To a solution of (S)-3-(3-bromo-phenyl)-2-*tert*-butoxycarbonylamino-propionic acid (500 mg, 1.45 mmol) in THF (30 mL) was added borane-tetrahydrofuran complex (1.0 M solution) (4.35 mL, 4.35 mmol). The reaction mixture was stirred at room temperature for 14 h and quenched with acetic acid (1 mL). After removal of most
15 solvent, the residue was extracted with EtOAc, washed with brine, dried over Na_2SO_4 . After concentration, the crude product (400 mg, 83%) was used for the next step without purification. LCMS ($\text{M}+\text{H}$) $^+$ m/z 330 ($t = 1.61$ min)

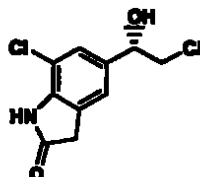


20

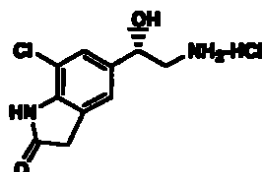
- (S)-2-Amino-3-(3-bromo-phenyl)-propan-1-ol:** To a solution of (S)-[2-(3-bromo-phenyl)-1-hydroxymethyl-ethyl]-carbamic acid *tert*-butyl ester (400 mg, 1.21 mmol) in methanol (30 mL) was added 4 M HCl in dioxane (2 mL, excess). The reaction mixture was stirred at room temperature for 14 h. After concentration *in vacuo*, the
25 residue was used for the next step without purification. LCMS ($\text{M}+\text{H}$) $^+$ m/z 230 ($t = 0.78$ min.)



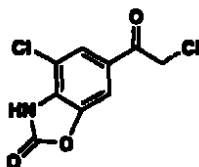
- 5-Chloroacetyl-7-chlorooxindole:** To a suspension of AlCl_3 (13.4g, 0.10 mol) in methylene chloride (40mL) is added a solution of 7-Chlorooxindole (0.10 mol) and chloroacetyl chloride (8 mL, 0.10 mol) at 0°C . The solution is warmed to ambient temperature for two hours and poured onto ice and extracted with methylene chloride, washing with saturated bicarbonate solution, brine, and drying over MgSO_4 would provide the desired chloroketone.



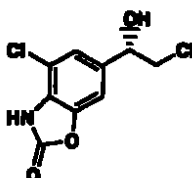
- (S)-7-Chloro-5-(2-chloro-1-hydroxy-ethyl)-2-oxindole :** To a solution of (S)-Methyl-CBS-oxazaborolidine (1M in toluene, 0.745 mL, 0.745 mmol) and $\text{BH}_3\text{-THF}$ (8mL, 8 mmol) is added at the same time a solution of $\text{BH}_3\text{-THF}$ (19mL, 19 mmol) and a solution of the 5-Chloroacetyl-7-chlorooxindole (37.98 mmol) in 19 mL of THF. Both solutions are added dropwise over 30 minutes. The solution is stirred for 1 hour and quenched with the slow addition of methanol (50mL). The solution is concentrated and the residue chromatographed over a short silica gel column (1:1 hexane/ethyl acetate).



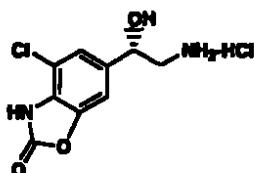
- (S)-2-Amino-1-(7-chlorooxindole-5-yl)-ethanol Hydrochloride :** To a solution of the chlorohydrin (37.9 mmol) in 120 mL of methanol at -40°C is added 100 grams of ammonia. The solution is sealed in a pressure bottle and warmed to ambient temperature and stirred for 48 hours. The solution is cooled and opened. The ammonia is allowed to evaporate and solution concentrated to provide the hydrochloride salt, which can be crystallized from ethanol/ethyl acetate.



6-Chloroacetyl-4-chloro-2-benzooxazolinone: To a suspension of AlCl_3 (13.4g, 0.10 mol) in methylene chloride (40mL) is added a solution of 4-chloro-2-benzooxazolinone (0.10 mol) and chloroacetyl chloride (8 mL, 0.10 mol) at 0°C . The solution is warmed to ambient temperature for two hours and poured onto ice and extracted with methylene chloride, washing with saturated bicarbonate solution, brine, and drying over MgSO_4 would provide the desired chloroketone.

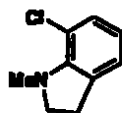


(S)-6-(2-Chloro-1-hydroxy-ethyl)-4-chloro-2-benzooxazolinone: To a solution of (S)-Methyl-CBS-oxazaborolidine (1M in toluene, 0.745 mL, 0.745 mmol) and BH_3 -THF (8mL, 8 mmol) is added at the same time a solution of BH_3 -THF (19mL, 19 mmol) and a solution of the 6-Chloroacetyl-4-chloro-2-benzooxazolinone (37.98 mmol) in 19 mL of THF. Both solutions are added dropwise over 30 minutes. The solution is stirred for 1 hour and quenched with the slow addition of methanol (50mL). The solution is concentrated and the residue chromatographed over a short silica gel column (1:1 hexane/ethyl acetate).



(S)-2-Amino-1-(4-chloro-2-benzooxazolinone-6-yl)-ethanol Hydrochloride : To a solution of the chlorohydrin (37.9 mmol) in 120 mL of methanol at -40°C is added 100 grams of ammonia. The solution is sealed in a pressure bottle and warmed to

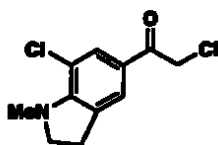
ambient temperature and stirred for 48 hours. The solution is cooled and opened. The ammonia is allowed to evaporate and solution concentrated to provide the hydrochloride salt, which can be crystallized from ethanol/ethyl acetate.



5

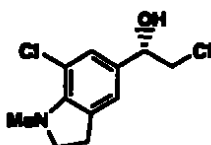
N-Methyl-7-chloroindoline: To a solution of the 7-Chloroindoline (0.10 mol) in 500 mL of acetone is added K_2CO_3 (0.15mol) and MeI (0.15mol) and refluxed until the starting material is consumed. The reaction is filtered and washed with water and saturated bicarbonate solution, drying over $MgSO_4$ would provide the N-Me-7-chloroindoline

10



N-Methyl-5-chloroacetyl-7-chloro-indoline: To a suspension of $AlCl_3$ (13.4g, 0.10 mol) in methylene chloride (40mL) is added a solution of N-Me-7-Chloroindoline (0.10 mol) and chloroacetyl chloride (8 mL, 0.10 mol) at $0^\circ C$. The solution is warmed to ambient temperature for two hours and poured onto ice and extracted with methylene chloride, washing with saturated bicarbonate solution, brine, and drying over $MgSO_4$ provides the desired chloroketone.

20

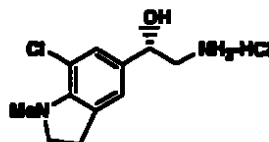


(S)-N-Methyl-5-(2-chloro-1-hydroxyethyl)-7-chloro-indoline: To a solution of (S)-Methyl-CBS-oxazaborolidine (1M in toluene, 0.745 mL, 0.745 mmol) and BH_3 -THF (8mL, 8 mmol) is added at the same time a solution of BH_3 -THF (19mL, 19 mmol) and a solution of N-Methyl-5-chloroacetyl-7-chloro-indoline (37.98 mmol) in 19 mL of THF. Both solutions are added dropwise over 30 minutes. The solution is

25

25

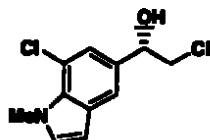
stirred for 1 hour and quenched with the slow addition of methanol (50mL). The solution is concentrated and the residue chromatographed over a short silica gel column (1:1 hexane/ethyl acetate).



5

(S)-2-Amino-1-(7-chloro-N-methyl-indoline-5-yl)-ethanol Hydrochloride : To a solution of the chlorohydrin (37.9 mmol) in 120 mL of methanol at -40°C is added 100 grams of ammonia. The solution is sealed in a pressure bottle and warmed to ambient temperature and stirred for 48 hours. The solution is cooled and opened. The ammonia is allowed to evaporate and solution concentrated to provide the hydrochloride salt, which can be crystallized from ethanol/ethyl acetate.

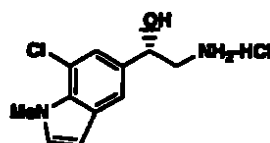
10



15

(S)-2-Chloro-1-(7-chloro-N-methyl-indol-5-yl)-ethanol: A solution (S)-N-Methyl-5-(2-chloro-1-hydroxyethyl)-7-chloro-indoline (0.10 mmol) in 100mL of t-butyl methyl ether is treated with o-chloroanil (0.10mmol) at ambient temperature. The solution is concentrated and the residue chromatographed over silica gel (1:1 hexane/ethyl acetate) to provide the corresponding indole.

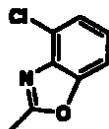
20



(S)-2-Amino-1-(7-chloro-N-methyl-indol-5-yl)-ethanol Hydrochloride : To a solution of the chlorohydrin (37.9 mmol) in 120 mL of methanol at -40°C is added 100 grams of ammonia. The solution is sealed in a pressure bottle and warmed to ambient temperature and stirred for 48 hours. The solution is cooled and opened.

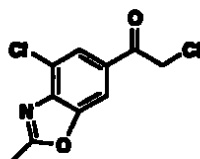
25

The ammonia is allowed to evaporate and solution concentrated to provide the hydrochloride salt, which can be crystalized from ethanol/ethyl acetate.



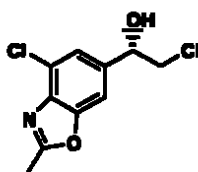
5

4-Chloro-2-methyl-benzooxazole : To a solution of the 4-chloro-2-benzooxazolinone (0.10 mol) in 200 mL ethanol is added LiOH (0.20 mol) in 100 mL of water. The solution is refluxed for 8 hr and cooled. The solution is neutralized with 1N HCl and extracted with ethyl acetate followed by drying over MgSO₄. The solution is concentrated and taken up in 200 mL of toluene and 0.10 mol of acetic acid. The solution is refluxed in a Dean Stark trap for 12 hours, concentrated and purified by flash chromatography.



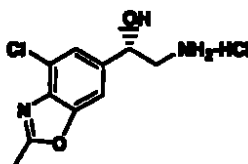
15

6-Chloroacetyl-4-chloro-2-methyl-benzooxazole: To a suspension of AlCl₃ (13.4g, 0.10 mol) in methylene chloride (40mL) is added a solution of 2-Methyl-4-chloro-benzooxazole (0.10 mol) and chloroacetyl chloride (8 mL, 0.10 mol) at 0°C. The solution is warmed to ambient temperature for two hours and poured onto ice and extracted with methylene chloride, washing with saturated bicarbonate solution, brine, and drying over MgSO₄ would provide the desired chloroketone.



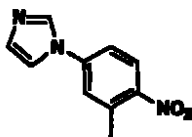
(S)-6-(2-chloro-1-hydroxy-ethyl)-4-chloro-2-methyl-benzooxazole: To a solution of (S)-Methyl-CBS-oxazaborolidine (1M in toluene, 0.745 mL, 0.745 mmol) and

BH₃-THF (8mL, 8 mmol) is added at the same time a solution of BH₃-THF (19mL, 19 mmol) and a solution of 6-Chloroacetyl-4-chloro-2-methyl-benzooxazole (37.98 mmol) in 19 mL of THF. Both solutions are added dropwise over 30 minutes. The solution is stirred for 1 hour and quenched with the slow addition of methanol (50mL). The solution is concentrated and the residue chromatographed over a short silica gel column (1:1 hexane/ethyl acetate).



(S)-2-Amino-1-(4-chloro-2-methyl-benzooxazol-6-yl)-ethanol Hydrochloride : To a solution of the chlorohydrin (37.9 mmol) in 120 mL of methanol at -40°C is added 100 grams of ammonia. The solution is sealed in a pressure bottle and warmed to ambient temperature and stirred for 48 hours. The solution is cooled and opened. The ammonia is allowed to evaporate and solution concentrated to provide the hydrochloride salt, which can be crystallized from ethanol/ethyl acetate.

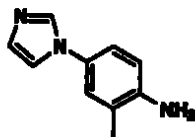
Preparation of 3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-iodo-1H-pyridin-2-one:



20

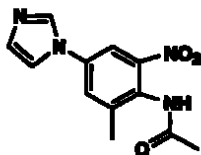
1-(3-Methyl-4-nitro-phenyl)-1H-imidazole: To a solution of 4-fluoro-2-methyl-1-nitro-benzene (300 mg, 1.84 mmol) in DMSO (2 mL) were added KOH (20 mg, 3.87 mmol) and imidazole (263 mg, 3.88 mmol). The reaction mixture was heated to 100°C for 3.5 h, cooled to room temperature, and diluted with ice-cold water. The resulting precipitate was filtered, washed with ice-cold water, and dried under vacuum to give the title compound (310 mg, 80%) as a yellow powder. ¹H NMR (300 MHz,

DMSO- d_6) δ 8.46 (1H, s), 8.16 (1H, d, $J = 8.9$ Hz), 7.90 – 7.92 (2H, m), 7.78 (1H, dd, $J = 2.5, 8.9$ Hz), 7.17 (1H, s), 2.61 (3H, s). LRMS (M+H) $^+$ m/z 204.



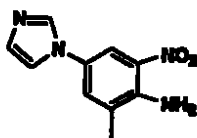
5

4-Imidazol-1-yl-2-methyl-phenylamine: To 1-(3-methyl-4-nitro-phenyl)-1H-imidazole (200 mg, 0.98 mmol) and 10% Palladium on carbon (35 mg) was added degassed methanol (3 mL). The suspension was flushed and evacuated with hydrogen / vacuum line. The suspension was allowed to stir at room temperature for 14 h under
10 hydrogen atmosphere (hydrogen balloon). The dark reaction mixture was filtered through a pad of celite and rinsed with methanol. Concentration of the filtrate gave the title compound (166 mg, 98%) which was used for the next step without purification. ^1H NMR (300 MHz, DMSO- d_6) δ 7.95 (1H, s), 7.48 (1H, s), 7.16 (1H, narrow d, $J = 2.5$ Hz), 7.09 (1H, dd, $J = 2.5, 8.4$ Hz), 7.01 (1H, s), 6.67 (1H, d, $J = 8.4$
15 Hz), 5.03 (2H, broad s), 2.10 (3H, s).

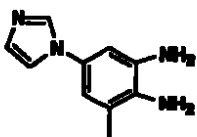


N-(4-Imidazol-1-yl-2-methyl-6-nitro-phenyl)-acetamide: To a solution of 4-imidazol-1-yl-2-methyl-phenylamine (1 g, 5.78 mmol) in CH_2Cl_2 (20 mL) was added Ac_2O (0.7 mL, 7.28 mmol) at 0°C . The reaction mixture was stirred at room temperature for 14 h and diluted with water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give a white solid. The white solid was
25 suspended in H_2SO_4 (conc.) (15 mL). Then HNO_3 (conc.) (0.312 mL) was added to the suspension at 0°C . The reaction mixture was slowly warmed to room temperature and stirred at room temperature for 4 h. After cooling to -10°C , the reaction mixture was neutralized with ammonium hydroxide and extracted with ethyl acetate. The

combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated. The residue was purified by flash chromatography (1:9:5 MeOH / THF / hexane) to yield the title compound (0.61 g, 41%). ^1H NMR (300 MHz, CD_3OD) δ 8.11 (1H, s), 7.45 – 7.56 (2H, m), 7.38 (1H, dd, $J = 2.4, 8.4$ Hz), 7.14 (1H, s), 2.33 (3H, s), 2.18 (3H, s).

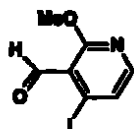


4-Imidazol-1-yl-2-methyl-6-nitro-phenylamine: To a suspension of *N*-(4-imidazol-1-yl-2-methyl-6-nitro-phenyl)-acetamide (279 mg, 1.07 mmol) in ethanol (3 mL) was added 2 N HCl (2 mL). The reaction mixture was heated to reflux for 14 h, cooled to room temperature, and neutralized with saturated NaHCO_3 . The resulting bright orange solid was filtered and dried under vacuum. The title compound (179 mg, 76%) was obtained as an orange solid. ^1H NMR (300 MHz, CD_3OD) δ 8.78 (1H, s), 8.24 (1H, s), 7.78 (1H, s), 7.64 (1H, s), 7.46 (1H, s), 2.36 (3H, s).



5-Imidazol-1-yl-3-methyl-benzene-1,2-diamine: To 4-imidazol-1-yl-2-methyl-6-nitro-phenylamine (350 mg, 1.61 mmol) and 10% Palladium on carbon (40 mg) were added degassed methanol (5 mL) and TFA (5 drops). The reaction mixture was flushed and evacuated with hydrogen / vacuum line, stirred at room temperature for 14 h under hydrogen atmosphere (hydrogen balloon). The dark reaction mixture was filtered through a pad of celite and rinsed with methanol. Concentration of the filtrate gave the residue, which was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with saturated NaHCO_3 , brine, dried over Na_2SO_4 . Concentration to dryness gave the title compound (275 mg, 91%) as a solid. ^1H NMR (300 MHz, CD_3OD) δ 7.87 (1H, s), 7.34 (1H, s), 7.05 (1H, s), 6.72 (1H, d, J

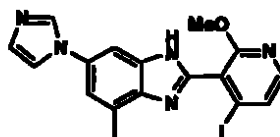
= 2.4 Hz), 6.65 (1H, d, J = 2.4 Hz) 2.21 (3H, s). LCMS (M+H)⁺ m/z 189 (t = 0.23 min.).



5

4-Iodo-2-methoxy-pyridine-3-carbaldehyde (WO 95/29917): A 5-liter three-necked round bottom flask was equipped with an overhead mechanical stirrer under nitrogen, the flask was charged with THF (1 L) and cooled to -78°C. To this stirred solution was added *tert*-butyllithium (1.7 M solution in pentane) (800 mL, 1.36 mol) via
10 canula followed by 2-methoxypyridine (132.2 g, 1.21 mol) at -78°C. The mixture was stirred for 1 h at -78°C. To the mixture was added *N*-formyl-*N*, *N'*, *N'*-trimethylethylenediamine (176 mL, 1.37 mol) dropwise at -78°C. The reaction mixture was stirred for ca. 30 min at -78°C before warming to -23°C over ca. 30 min. To the mixture at -23°C was added ethylene glycol dimethyl ether (1 L) followed by
15 *n*-butyllithium (2.5 M solution in hexane) (800 mL, 2.0 mol). The resulting mixture was stirred for ca. 2 h during which time the reaction mixture turned deep green. A 12-L 4-necked round flask was charged with iodine (571 g, 2.25 mol) and ethylene glycol dimethyl ether (2 L) and the resultant solution was cooled to -78°C. The contents of the 5-L flask were transferred via canula to the mixture of iodine and
20 ethylene glycol dimethyl ether in the 12-L flask at -78°C. After the addition was complete, the reaction mixture was stirred for an additional 1 h at -78°C. The cooling bath was removed and the mixture was allowed to warm to about 0°C and treated with 2 L of water and 2 L of 1 N hydrochloric acid. Methyl *t*-butyl ether (2L) was added and the layers were separated. The aqueous layer was extracted with 2 x 1 L of methyl
25 *t*-butyl ether. The combined organic layers were washed with saturated Na₂S₂O₃ (1.2 L), brine (1.2 L), dried over Na₂SO₄. After concentration *in vacuo*, the thick slurry was diluted with hexane (1 L). The mixture was cooled with an ice / water bath for ca. 30 min. The precipitate was filtered and dried in vacuum to yield the title compound as a light yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 10.22 (s, 1H), 7.86 (1H, d, J =

5.3 Hz), 7.54 (1H, d, $J = 5.3$ Hz), 4.06 (3H, s). LCMS ($M+H$)⁺ m/z 364 ($t = 2.26$ min.).

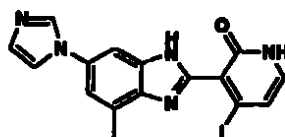


5

6-Imidazol-1-yl-2-(4-iodo-2-methoxy-pyridin-3-yl)-4-methyl-1H-benzimidazole:

To a solution of 5-imidazol-1-yl-3-methyl-benzene-1,2-diamine (175 mg, 0.93 mmol) in methanol (8 mL) was added a solution of 4-iodo-2-methoxy-pyridine-3-carbaldehyde (245 mg, 0.93 mmol) in methanol (5 mL) at 0°C. The reaction mixture was stirred at 0°C for 1.5 h and then at room temperature for 2 h. After concentration, the residue was purified by flash column chromatography (10% MeOH / CH₂Cl₂) to give the title compound (291 mg, 60%). ¹H NMR (300 MHz, CD₃OD) δ 8.13 (1H, s), 7.98 (1H, d, $J = 5.4$ Hz), 7.62 (1H, d, $J = 5.4$ Hz), 7.59 (2H, s), 7.33 (1H, s), 7.16 (1H, s), 3.90 (3H, s), 2.67 (3H, s). LCMS ($M+H$)⁺ m/z 432 ($t = 0.99$ min.).

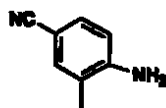
15



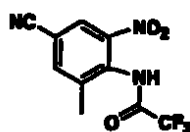
3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-iodo-1H-pyridin-2-one:

The suspension of 6-imidazol-1-yl-2-(4-iodo-2-methoxy-pyridin-3-yl)-4-methyl-1H-benzimidazole in 1 N HCl (6 mL) was heated to 70°C for 3 days, cooled to room temperature, and diluted with ethyl acetate. After extraction, the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (1% NH₄OH / 10% MeOH / CH₂Cl₂) to yield the title compound (78 mg, 81%) as a solid. ¹H NMR (300 MHz, CD₃OD) δ 8.12 (1H, s), 7.58 (2H, s), 7.29 – 7.31 (2H, m), 7.16 (1H, s), 7.01 (1H, $J = 6.8$ Hz), 2.66 (3H, s). LCMS ($M+H$)⁺ m/z 418 ($t = 0.75$ min.).

Preparation of 2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazole-5-carbonitrile:

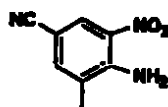


4-Amino-3-methyl-benzonitrile: To a solution of 3-methyl-4-nitro-benzonitrile (20 g, 0.123 mol) in HOAc (200 mL) was added iron powder (17.55 g, 0.309 mol). After 10 min, the reaction was exothermic and turned to dark color. The reaction mixture was allowed to stir at room temperature for 14 h and then diluted with EtOAc (200 mL). The brown precipitate was filtered through a pad of celite and the filtercake was rinsed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was
10 purified by flash chromatography (40% EtOAc / hexane) to yield the title compound (15.3 g, 92%). ¹H NMR (300 MHz, CDCl₃) δ 7.30 – 7.34 (2H, m), 6.64 (1H, d, *J* = 8.7 Hz), 2.16 (3H, s). LCMS (M+H)⁺ *m/z* 133 (*t* = 0.93 min).

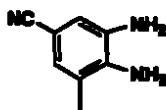


15

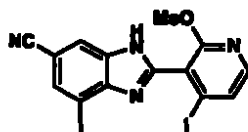
***N*-(4-Cyano-2-methyl-6-nitro-phenyl)-2,2,2-trifluoro-acetamide:** To the ice-cold trifluoroacetic anhydride (60 mL) was added 4-amino-3-methyl-benzonitrile (14.33 g, 0.108 mol) in portion. The resulting white slurry was stirred at 0°C for 30 min. Then ammonium nitrate (17.28 g, 0.216 mol) was added. The reaction mixture was allowed
20 to stir at 0°C for 1 h and at room temperature for 14 h. After removal of most solvent, the reaction mixture was cooled with ice and quenched with ice. The yellow precipitate was filtered, washed with cold water, and dried under vacuum. The crude product (15.5 g, 52% yield, and ca. 80% pure) was used for the next step without purification. ¹H NMR (300 MHz, CD₃OD) δ 8.05 (1H, s), 7.74 (1H, s), 2.30 (3H, s).
25 LRMS (neg. ESI, (M-H)⁻) *m/z* 272.



4-Amino-3-methyl-5-nitro-benzonitrile: A mixture of *N*-(4-cyano-2-methyl-6-nitro-phenyl)-2,2,2-trifluoro-acetamide (5 g, 18.3 mmol) and 2 M ammonia in methanol (80 mL) was heated to reflux for 14 h and then cooled to room temperature. After concentration *in vacuo*, the residue was purified by flash chromatography (20% EtOAc / hexane) to yield the title compound (3.24 g, 100%, ca 80% pure). ¹H NMR (300 MHz, CDCl₃) δ 8.40 (1H, s), 7.47 (1H, s), 6.6 – 6.8 (2H, broad s), 2.89 (3H, s).

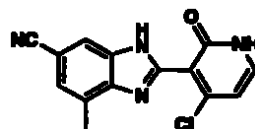


3,4-Diamino-5-methyl-benzonitrile: To a solution of 4-amino-3-methyl-5-nitro-benzonitrile (3.24 g, 18.3 mmol) in ethanol (80 mL) was added tin chloride dihydrate (8.67 g, 49.75 mmol). The reaction mixture was heated to reflux for 14 h, then cooled to room temperature, and concentrated *in vacuum*. The residue was diluted with ethyl acetate (100 mL) and treated with triethylamine (20 mL). The resulting slurry was filtered through a pad of celite and the filtercake was rinsed with three-portion ethyl acetate (50 mL). The filtrate was washed with saturated NaHCO₃, water, and brine, then dried over Na₂SO₄ and filtered. After removal of solvent, the residue was purified by flash chromatography on silica gel (30% - 50% EtOAc / hexane) to yield the title compound (2.17 g, 81%) as a light yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 6.94 (1H, s), 6.85 (1H, s), 2.16 (3H, s). LCMS (M+H)⁺ m/z 148 (t = 0.67 min.).



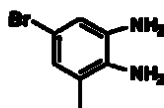
2-(4-Iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzimidazole-5-carbonitrile: To a solution of 3,4-diamino-5-methyl-benzonitrile (2.00 g, 13.6 mmol) in MeOH (40 mL) was added 4-iodo-2-methoxy-pyridine-3-carbaldehyde (3.6 g, 13.6 mmol) in MeOH (20 mL) at 0°C. The resulting slurry was stirred at 0°C for 1 h. Iodine (1.73 g, 8.8 mmol) in MeOH (10 mL) was added dropwise *via* a dropping funnel to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 14

- h. After removal of MeOH, the residue was diluted with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 . The crude product was purified by flash column chromatography (3% MeOH / CH_2Cl_2) to yield the title compound (1.81 g, 46%). ^1H NMR (300 MHz, CDCl_3) δ 7.90 (1H, s), 7.49 (1H, d, $J = 5.4$ Hz), 7.46 (1H, s), 7.41 (1H, d, $J = 5.3$ Hz), 3.78 (3H, s), 2.68 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 391 ($t = 1.27$ min.).



- 2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazole-5-carbonitrile: A suspension of 2-(4-iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzimidazole-5-carbonitrile (1.8 g, 4.63 mmol) in 4 M HCl dioxane (40 mL) was heated to 80°C for 6 h and cooled to room temperature. The precipitate was filtered and dried. The crude product (1.08 g, 82%) was used for the next step without purification. LRMS (neg. ESI, $(\text{M}-\text{H})^-$) m/z 283.

Preparation of (S)-4-(1-Benzyl-2-trityloxy-ethylamino)-3-(6-bromo-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;



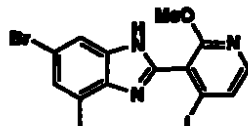
20

- 5-Bromo-3-methyl-benzene-1,2-diamine:** To a suspension of 4-bromo-2-methyl-6-nitro-phenylamine (20 g, 0.086 mol) in ethanol (200 mL) was added tin chloride dihydrate (49.2 g, 0.258 mol). The reaction mixture was heated to reflux for 14 h, cooled to room temperature, and concentrated *in vacuo*. The residue was diluted with ethyl acetate (150 mL) and treated with triethylamine (40 mL). The resulting slurry was filtered through a pad of celite, and the filtercake was rinsed with three portions ethyl acetate (50 mL). The filtrate was washed with saturated NaHCO_3 , water, and brine, then dried over Na_2SO_4 and filtered. After removal of the solvent, the residue

30

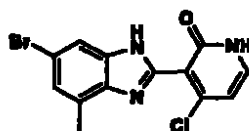
was purified by flash chromatography on silica gel (30% EtOAc / hexane, then 5% MeOH / CH₂Cl₂) to yield the title compound (10.26 g, 59%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 6.77 (1H, d, *J* = 2.0 Hz), 6.74 (1H, d, *J* = 2.0 Hz), 2.16 (3H, s). LCMS (M+H)⁺ *m/z* 201. (*t* = 0.83 min.).

5



6-Bromo-2-(4-iodo-2-methoxy-pyridin-3-yl)-4-methyl-1H-benzimidazole: To a solution of 5-bromo-3-methyl-1,2-phenylenediamine (4 g, 19.9 mmol) in methanol (80 mL) was added 4-iodo-2-methoxy-pyridine-3-carbaldehyde (5.23 g, 19.9 mmol) in methanol (20 mL) dropwise at 0°C. The resulting slurry was stirred for 30 min at room temperature. Then iodine (2.53 g, 9.95 mmol) in methanol (20 mL) was added via a dropping funnel. After 14 h, the reaction mixture was concentrated *in vacuo*, diluted with 5% Na₂S₂O₃, and extracted with ethyl acetate. The combined organic layers were washed with water, brine, and dried over Na₂SO₄. After removal of solvent, the residue was purified by careful flash chromatography (20% EtOAc / hexane) to yield the title compound (4.05 g, 46%) as a yellow foam. ¹H NMR (300 MHz, CDCl₃) δ 7.86 (1H, d, *J* = 5.31 Hz), 7.53 (1H, d, *J* = 5.3 Hz), 7.26 (2H, broad s), 3.91 (3H, s), 2.63 (3H, s). LCMS (M+H)⁺ *m/z* 444 (*t* = 1.39 min.).

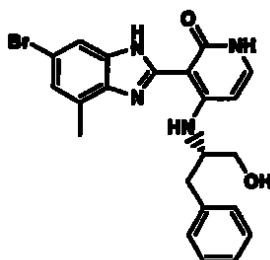
20



3-(6-Bromo-4-methyl-1H-benzimidazol-2-yl)-4-chloro-1H-pyridin-2-one: The suspension of 6-bromo-2-(4-iodo-2-methoxy-pyridin-3-yl)-4-methyl-1H-benzimidazole (4 g, 9.03 mmol) and 60 mL of 4 M HCl in dioxane was heated to 80°C for 6 h and cooled to room temperature. The precipitate was filtered and dried to yield the title compound (3.0 g, 100%) as a brown powder. The crude product was used for the next step without purification. ¹H NMR (300 MHz, CD₃OD) δ 7.55 (1H,

25

s), 7.42 (1H, d, $J = 6.0$ Hz), 7.17 (1H, s), 6.91 (1H, d, $J = 6.0$ Hz), 2.55 (3H, s). LC MS (M+H)⁺ m/z 338 ($t = 1.33$ min.).

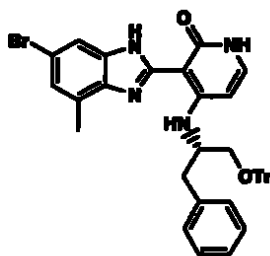


5

(S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(6-bromo-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: To a solution of 3-(6-bromo-4-methyl-1H-benzimidazol-2-yl)-4-chloro-1H-pyridin-2-one (1.42 g, 3.78 mmol) in DMF (15 mL) were added (S)-(-)-2-amino-3-phenyl-1-propanol (1.43 g, 9.45 mmol) and *N*-methyl morpholine (1.5

10 mL). The reaction mixture was heated to 80°C for 6 h and cooled to room temperature. The solvent was removed with high vacuum and the residue was purified by flash chromatography (5% MeOH / CH₂Cl₂) to yield the title compound (1.26 g, 74%) as a yellow foam. ¹H NMR (300 MHz, CDCl₃) δ 6.9 – 7.2 (8H, m), 5.86 (1H, d, $J = 7.1$ Hz), 3.7-3.9 (3H, m), 2.9-3.1 (2H, m), 2.57 (3H, s). LCMS (M+H)⁺ m/z 453 ($t = 2.03$ min.).

15



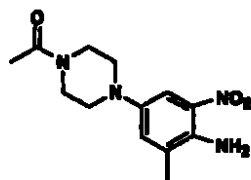
(S)-4-(1-Benzyl-2-trityloxy-ethylamino)-3-(6-bromo-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: To a solution of (S)-4-(1-benzyl-2-hydroxy-ethylamino)-3-(6-bromo-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one (0.9 g, 1.98 mmol) in THF (30 mL), was added Cs₂CO₃ (1.29 g, 3.96 mmol) followed by triphenylmethyl chloride (1.10 g, 3.96 mmol). The reaction mixture was heated to reflux for 14 h under nitrogen and then cooled to room temperature. After removal of the solvent, the

20 residue was diluted with ethyl acetate and washed with water. The aqueous fraction

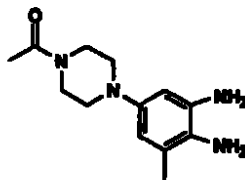
25

was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried over Na_2SO_4 . After concentration *in vacuo*, the residue was purified by flash column chromatography (30% EtOAc / hexane) to yield the title compound (1 g, 73%) as a white solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.77 (1H, broad s), 11.73 (1H, d, $J = 5.2$ Hz), 11.46 (1H, broad s), 7.13 – 7.54 (23H, m), 5.87 (1H, d, $J = 4.5$ Hz), 4.09 – 4.14 (1H, m), 3.07 – 3.42 (4H, m), 2.54 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 695 ($t = 2.79$ min.).

Preparation of 3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-chloro-1H-pyridin-2-one:

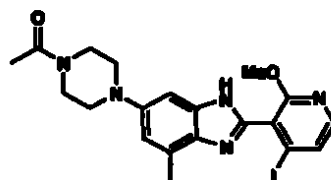


1-[4-(4-Amino-3-methyl-5-nitro-phenyl)-piperazin-1-yl]-ethanone: A mixture of 4-bromo-2-methyl-6-nitro-phenylamine (5g, 21.64 mmol), 1-acetylpiperazine (4.2g, 32.46 mmol), palladium acetate (244 mg, 1.08 mmol), tri-*tert*-butylphosphine (440 mg, 2.16 mmol) and sodium *tert*-butoxide (4.2 g, 43.29 mmol) in toluene (70 mL) was heated to 100°C for 14 h under nitrogen. The reaction mixture was cooled to room temperature and diluted with EtOAc. After extraction, the combined organic layers were washed with water, brine, dried over Na_2SO_4 . Concentration gave a brownish residue which was purified by flash column chromatography (10% MeOH / CH_2Cl_2) to yield the title compound (4.21 g, 70%). ^1H NMR (400 MHz, CD_3OD) δ 7.42 (1H, d, $J = 2.8$ Hz), 7.23 (1H, d, $J = 2.8$ Hz), 3.71 (2H, t, $J = 5.1$ Hz), 3.67 (2H, t, $J = 5.1$ Hz), 3.04 (2H, t, $J = 5.2$ Hz), 2.98 (2H, t, $J = 5.2$ Hz), 2.24 (3H, s), 2.13 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 279 ($t = 1.46$ min.).



1-[4-(3,4-Diamino-5-methyl-phenyl)-piperazin-1-yl]-ethanone: To 1-[4-(4-amino-3-methyl-5-nitro-phenyl)-piperazin-1-yl]-ethanone (4.5 g, 16.2 mmol) and 10% palladium on carbon (400 mg) were added methanol (50 mL) and acetic acid (5 mL) under nitrogen.

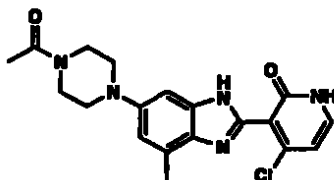
- 5 The reaction mixture was stirred under hydrogen atmosphere (hydrogen balloon) for 14 h. The dark solution was filtered through a pad of celite and the filtercake was washed with methanol. Concentration of the filtrate gave the title compound (4.00 g, 100%) which was used for the next step without purification. LCMS (M+H)⁺ m/z 207 (t = 0.41 min.).



10

1-[4-[2-(4-Iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl]-piperazin-1-yl]-ethanone: To a solution of 1-[4-(3,4-diamino-5-methyl-phenyl)-piperazin-1-yl]-ethanone (4.00 g, 16.18 mmol) in methanol (100 mL) was added 4-iodo-2-methoxy-

- 15 pyridine-3-carbaldehyde (4.25 g, 16.18 mmol). The reaction mixture was stirred at room temperature for 14 h. After concentration, the residue was purified by flash column chromatography (10% MeOH / CH₂Cl₂) to yield the title compound (5.25 g, 66%). ¹H NMR (400 MHz, CD₃OD) δ 7.81 (1H, d, J = 5.4 Hz), 7.48 (1H, d, J = 5.4 Hz), 7.26 (1H, s), 6.85 (1H, s), 3.85 (3H, s), 3.78 (2H, t, J = 5.0 Hz), 3.64 (2H, t, J = 5.0 Hz), 3.16 (2H, t, J = 5.2 Hz), 3.11 (2H, t, J = 5.2 Hz), 2.62 (3H, s), 2.13 (3H, s). LCMS (M+H)⁺ m/z 492 (t = 1.71 min.).

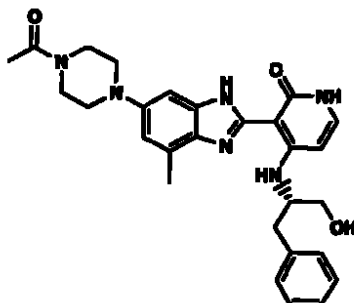


- 25 3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-chloro-1H-pyridin-2-one: To a solution of 1-[4-[2-(4-iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl]-piperazin-1-yl]-ethanone (5.2 g, 10.6 mmol) in 4 M HCl in

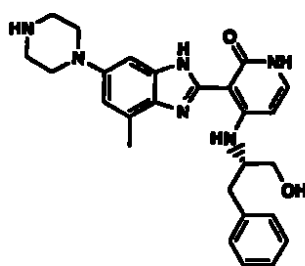
dioxane (60 mL) was added water (5 mL). The reaction mixture was stirred at room temperature for 14 h. Concentration of the reaction mixture gave the title compound (4.02 g, 100%) which was used for the next step without purification. LCMS (M+H)⁺ m/z 486 (t = 1.55 min.).

5

Preparation of (S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:

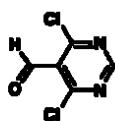


- 10 **(S)-3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one:** To a solution of 3-[6-(4-acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-chloro-1H-pyridin-2-one (1 g, 2.6 mmol) in DMF (10 mL) was added (S)-(-)-2-amino-3-phenyl-propanol (0.78 mg, 5.2 mmol) and *N*-methyl morpholine (2 mL). The reaction mixture was heated to 80°C for 12
- 15 h, cooled to room temperature and concentrated with high vacuum. The residue was purified by flash column chromatography (10% MeOH / CH₂Cl₂) to yield the title compound (0.90 g, 69%). ¹H NMR (400 MHz, CD₃OD) δ 7.36 (1H, s), 7.02 – 7.23 (6H, m), 6.80 (1H, s), 5.98 (1H, d, *J* = 7.5 Hz), 4.10 – 4.12 (3H, m), 3.67 – 3.78 (6H, m), 3.06 – 3.11 (3H, m), 2.90 (1H, dd, *J* = 7.8, 13.6 Hz), 2.54 (3H, s), 2.12 (3H, s). LCMS (M+H)⁺
- 20 m/z 501 (t = 1.30 min.).



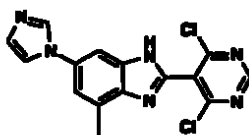
(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: To a solution of (S)-3-[6-(4-acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one (900 mg, 18 mmol) in 4 M HCl in dioxane (10 mL) was added
5 water (1 mL). The reaction mixture was heated to 80°C for 14 h and cooled to room temperature. Concentration with high vacuum gave the title compound (0.83 g, 100%) which was used for the next step without purification. LCMS (M+H)⁺ m/z 459 (t = 1.13 min.).

10 **Preparation of 2-(4,6-Dichloro-pyrimidin-5-yl)-6-imidazol-1-yl-4-methyl-1H-benzimidazole:**



15 **4,6-Dichloro-pyrimidine-5-carbaldehyde:** DMF (7 mL, 0.09 mol) was added to POCl₃ (21 mL, 0.23 mol) at 0°C. The reaction mixture was stirred at room temperature for 0.5 h. 4,6-Dihydroxy-pyrimidine-5-carbaldehyde (5 g, 0.045 mol) was added in small portions. The reaction mixture was heated to 90°C for 6 h and cooled to room temperature. A large excess of crushed ice was added to the reaction
20 mixture very slowly under ice-bath. The mixture was extracted with CH₂Cl₂. The combined organic layers were washed with water, brine, and dried over Na₂SO₄. After concentration, the residue was purified by column chromatography (20% EtOAc / hexane) to yield the title compound (4 g, 50%). ¹H NMR (400 MHz, CDCl₃) δ 8.91 (1H, s), 7.87 (1H, s). LRMS (M+H)⁺ m/z 177.

25

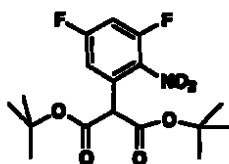


2-(4,6-Dichloro-pyrimidin-5-yl)-6-imidazol-1-yl-4-methyl-1H-benzimidazole: To a solution of 5-imidazol-1-yl-3-methyl-benzene-1,2-diamine (180 mg, 0.96 mmol) in

methanol (4 mL) was added a solution of 4,6-dichloro-pyrimidine-5-carbaldehyde (183 mg, 0.96 mmol) in methanol (1 mL). The reaction mixture was stirred at room temperature for 14 h. After concentration, the residue was purified by flash column chromatography (5% methanol / CH₂Cl₂) to yield the title compound (180 mg, 55%).

5 LCMS (M+H)⁺ m/z 344 (t = 1.31 min.).

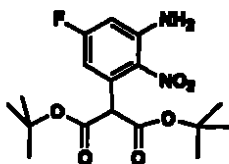
Procedure for the Preparation of 2-Amino-4-Fluoro-6-methyl nitrobenzene:



10

2-(3,5-Difluoro-2-nitro-phenyl)-malonic acid di-*tert*-butyl ester: To a suspension of NaH (54.6g, 60%, 1.365 mol) in 600mL of DMF was added di-*t*-Butyl malonate (118g, 0.546 mol) at 0°C and stirred for 30 min. 2,4,6 trifluoronitrobenzene was added as a solution in 400 mL of DMF (75 g, 0.42mol) over 3 hours and the solution stirred at ambient temperature for 12 hours. The reaction mixture was extracted with ethyl acetate (3X's). The ethyl acetate was washed with water (3X's) and with brine and dried over MgSO₄ and concentrated to give 62 g of crude product. LCMS [M+Na] - 396; ¹H NMR (500MHz, DMSO) δ 7.81 (m, 1H), 7.27 (m, 1H), 5.00 (s, 1H), 1.41 (m, 18H).

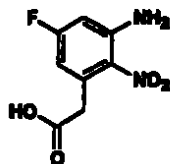
20



2-(3-Amino-5-fluoro-2-nitro-phenyl)-malonic acid di-*tert*-butyl ester: To the crude 2-(3,5-Difluoro-2-nitro-phenyl)-malonic acid di-*tert*-butyl ester (62g, 0.42 mol) was added 700 mL of 2M ammonia in methanol in a pressure bottle. The vessel was sealed and heated to 85°C for 18 hours. The reaction mixture was cooled and the vessel opened carefully and the methanol solution concentrated to provide 140 g of crude material. LCMS [M+Na] - 393; ¹H NMR (500MHz, DMSO) δ 6.76 (dd,

25

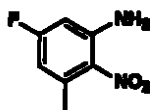
J=10.8 2.8Hz, 1H), 6.29 (dd, J=10.8, 2.8Hz, 1H), 4.99 (brs, 2H), 4.80 (s, 1H), 1.40 (m, 18H).



5

3-Amino-5-fluoro-2-nitro phenyl acetic acid: To the 2-(3-Amino-5-fluoro-2-nitro-phenyl)-malonic acid di-*tert*-butyl ester (140g) in 500 mL of 4N HCl in dioxane was added 50 mL of water and heated to 40°C for 2 days. The solution was extracted with ethyl acetate (3X's) and the ethyl acetate washed with water (3X's) and brine.

10 The organic fraction was dried over MgSO₄ and was concentrated to give 78g of crude (66% pure by LC/MS); ¹H NMR (500MHz, DMSO) δ 12.40 (brs, 1H), 7.04 (s, 2H), 6.68 (dd, J=10.9 2.8Hz, 1H), 6.47 (dd, J=10.9, 2.8Hz, 1H), 3.80 (s, 2H).

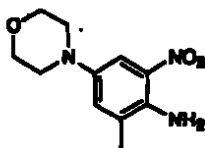


15

2-Amino-4-fluoro-6-methyl nitrobenzene: To the crude 3-Amino-5-fluoro-2-nitro phenyl acetic acid (3.6g, 16.8 mmol) was added Cu₂O (10.1g, 70.6 mmol) in 120 mL of acetonitrile along with 50uL of methanol and the suspension was refluxed for 12 hours. The reaction mixture was filtered through Celite and the Celite pad washed with water and ethyl acetate. The filtrate was extracted with ethyl acetate, washed with water and brine, dried over Na₂SO₄ and concentrated to give 2.95 g of material which by ¹H NMR was 80% pure. ESIMS [M+Na] – 193; ¹H NMR (500MHz, DMSO) δ 6.67 (s, 2H), 6.56 (dd, J=11, 2.8Hz, 1H), 6.39 (dd, J=11, 2.8Hz, 1H), 2.50 (s, 3H).

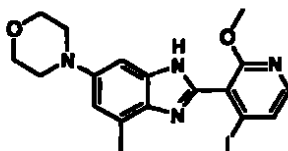
25

Procedure for the preparation of 4-Chloro-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one and 4-Iodo-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one



2-Methyl-4-morpholin-4-yl-6-nitro-phenylamine: To a 800 ml pressure flask was added Tris(dibenzylideneacetone)dipalladium (2.64 g, 2.88 mmol), 2-(Di-
5 butylphosphino)biphenyl (1.42 g, 4.75 mmol) and sodium tert-butoxide (17.5 g, 182 mmol). Then dry THF (500 mL), 4-bromo-2-methyl-6-nitroaniline (30.0 g, 130 mmol) and morpholine (34 ml, 390 mmol) were added. Argon was bubbled through the solution for 1 minute and the flask was sealed. The reaction mixture was stirred at 85 °C for 3 days. THF was evaporated *in vacuo* and the crude product was
10 preabsorbed on silica and this then transferred on top of a silica gel column. Elution with hexane-ethyl acetate (6:4 to 4:6 to 0:1 gradient) gave, after evaporation of solvents, the title compound (15.2 g red-brown solid, 49.3%). LCMS (M+H)⁺ m/z 238 (t = 0.64 min.) ¹H NMR (500 MHz, DMSO-d₆) δ 7.32 (1H, s), 7.22 (1H, s), 6.96 (2H, s), 3.72 (4H, broad s), 2.96 (4H, broad s), 2.21 (3H, s).

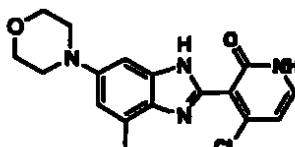
15



2-(4-Iodo-2-methoxy-pyridin-3-yl)-4-methyl-6-morpholin-4-yl-1H-benzimidazole:

20 2-Methyl-4-morpholin-4-yl-6-nitro-phenylamine (15.2 g, 64 mmol) was suspended in methanol (200 ml) in a PARR flask. Palladium on carbon (1.0 g, 10% Pd) was added and the suspension shaken under 60 psi of hydrogen overnight. The mixture was filtered through a pad of celite (under argon) into a 3-neck flask, the celite rinsed with methanol and the filtrate diluted with methanol to a total volume of 500 ml and cooled
25 to 0°C. A solution of 4-Iodo-2-methoxy-pyridine-3-carbaldehyde (14.6 g, 55.5 mmol) in methanol (500 ml) was added slowly (during 3 hours). After addition of ~ ¼ of the solution the system was opened to air and stirred over the weekend, thereby reaching room temperature. The reaction mixture was concentrated *in vacuo*, filtered through a

pad of silica (eluent: methylenechloride - ethyl acetate - methanol 55-40-5) then crystallized from ethyl acetate. The title compound was isolated as brown solid (12.68 g, 51%). Flash column chromatography of the mother liquor (gave additional 2.90 g (12%). [pack column with methylene chloride, elute compound with methylene chloride - ethyl acetate 6-4, then methylenechloride - ethyl acetate - methanol 58-40-2]. LCMS (M+H)⁺ m/z 451 (t = 1.03 min.). ¹H NMR (500 MHz, CDCl₃) δ 7.76 (1H, d, J = 5.3 Hz), 7.42 (1H, d, J = 5.3 Hz), 6.85 (1H, broad s), 6.82 (1H, s), 3.86 (4H, t, J = 4.5 Hz), 3.79 (3H, s), 3.12 (4H, t, J = 4.5 Hz), 2.60 (3H, s), 2.21 (3H, s).



10

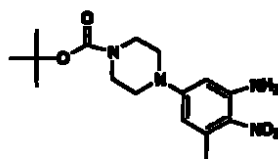
4-Chloro-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one and 4-Iodo-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one:

2-(4-Iodo-2-methoxy-pyridin-3-yl)-4-methyl-6-morpholin-4-yl-1H-benzoimidazole (15.58 g, 34.6 mmol) was suspended in 1,4-dioxane (300 ml) and conc. aqueous HCl (50 ml) was added. The mixture was stirred at ambient temperature overnight, then 3 hours at 50°C. The mixture was cooled to room temperature and poured into an ice cold solution of NaHCO₃ (67 g, 0.8 mol) and filtered. The aqueous phase was extracted with ethyl acetate. The solid material was dissolved in CH₂Cl₂ with some methanol, then extracted between water and CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, and concentrated *in vacuo* to give an inseparable mixture of the 4-Chloro- and 4-Iodo- title compounds. The product was used without further purification. LCMS (M+H)⁺ m/z 437 and m/z 345 (both t = 0.92 min.).

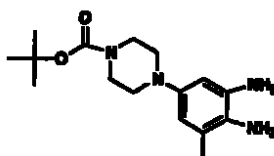
25

Procedure for the preparation of 4-[2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzoimidazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester and 4-[2-(4-Iodo-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzoimidazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester

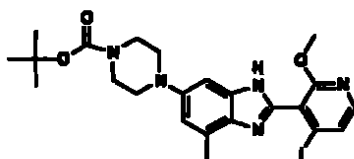
30



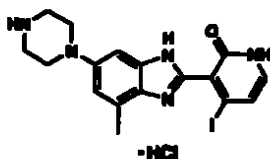
4-(3-Amino-5-methyl-4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester: To a stirred solution of 3-fluoro-5-amino-6-nitrotoluene (10 g, 58.79 mmol) in anhydrous NMP (160 mL) under nitrogen was added BOC-piperazine (39 g, 209.4 mmol) and 4-methylmorpholine (25.9 mL). The resulting dark solution was heated to reflux for 72 h, cooled to room temperature and diluted with ethyl acetate (4000 mL). The organic layer was washed with water (8 x 1500 mL), brine (1 x 1500 mL), dried over sodium sulfate and evaporated *in vacuo*. The resulting dark oil was dissolved in boiling absolute ethanol (800 mL) and concentrated to a total volume of 400 mL and left to stand overnight at room temperature. The solution was further cooled to -20 °C for 5 h and the resulting solid was filtered off and dried *in vacuo* to give 16.3 g (83%) of a light yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 6.16 (brs, 1H), 6.04 (brs, 1H), 3.70 – 3.60 (m, 4H), 3.38 – 3.25 (m, 4H), 2.53 (s, 3H), 1.48 (s, 9H); LCMS (M+H)⁺ m/z 337.



4-(3,4-Diamino-5-methyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester: To a stirred solution of 4-(3-Amino-5-methyl-4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (15 g, 44.6 mmol) in methanol (2200 mL) was added 20% Pd(OH)₂/C (1.6 g) and the suspension flushed well with nitrogen, followed by hydrogen. The resulting suspension was stirred overnight at room temperature under an atmosphere of hydrogen (ca. 1 atm). The resulting suspension was filtered under nitrogen through a pad of Celite and washed with methanol (400 - 500 mL). The resulting material was used immediately. LCMS (M+H)⁺ m/z 307.



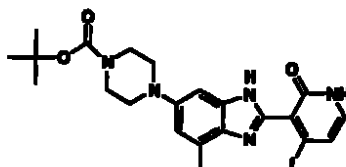
- 4-[2-(4-Iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzoimidazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester:** To a stirred solution of 4-(3,4-Diamino-5-methyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (44.6 mmol – assuming 100% conversion in previous step) in methanol (ca 2700 mL) at 0 °C under a nitrogen atmosphere was slowly added (2 h) via addition funnel, a solution of 4-iodo-2-methoxy-pyridine-3-carbaldehyde (15.0g, 57.1 mmol) in anhydrous methanol (225 mL). The resulting solution was then stirred at 0 °C for an additional 30 min., the cooling bath was removed, and the reaction mixture was allowed to stir at room temperature in the presence of air for 72 h. The resulting solution was concentrated *in vacuo* and the residue was dissolved in dichloromethane (1500 mL) and the solvent removed *in vacuo* (repeated 3x). The resulting dark foamy solid was dried under high vacuum. ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, 1H, J = 5.4 Hz), 7.50 (d, 1H, J = 5.4 Hz), 6.98 (brs, 1H), 6.90 (brs, 1H), 4.05 (s, 3H), 3.67 – 3.58 (m, 4H), 3.18 – 3.09 (m, 4H), 2.63 (s, 3H), 1.49 (s, 9H); LCMS (M+H)⁺ m/z 550.



- 4-Iodo-3-(4-methyl-6-piperazin-1-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one:** To a stirred solution of 4-[2-(4-Iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzoimidazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester (24g, 43.7 mmol) was added 1,4-dioxane (750 mL) and 6 N aqueous HCl (30 mL) and the mixture was heated to 75 °C overnight. The solution was cooled to room temperature, the supernatant was poured off, and the resulting dark gummy solid was washed with anhydrous diethyl ether (3 x 500 mL) and dried *in vacuo* to give 17.7 g (93%) of the title compound as a dark solid that was used as described to prepare 4-[2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzoimidazol-5-yl]-piperazine-1-

carboxylic acid tert-butyl ester and 4-[2-(4-Iodo-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester; LCMS (M+H)⁺ m/z 436. (Note: A small peak (4-chloro-pyridin-2-one) in the LC/MS shows m/z 344, 346).

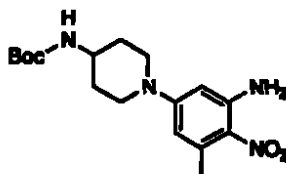
5



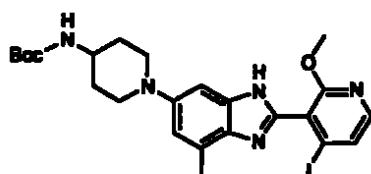
4-[2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester and 4-[2-(4-Iodo-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester: To a stirred suspension of 4-Iodo-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (17.7 g, 40.7 mmol) in dichloromethane (750 mL) was added di-*tert*-butyl dicarbonate (9.8 g, 44.8 mmol) and triethylamine (67.4 mL, 483.6 mmol). The mixture was stirred at room temperature for 30 min. and purified via flash chromatography on silica gel. After elution with dichloromethane followed by 2.5% methanol/ethyl acetate, homogeneous fractions were combined and partially evaporated *in vacuo* to give the product as a yellow solid, following filtration (8.9 g, ca 41%, 2 crops). ¹H NMR (500 MHz, CD₃OD) δ 7.25 (d, 1H, J = 6.9 Hz), 6.97 (d, 1H, J = 6.9 Hz), 6.97 (brs, 1H), 6.89 (brs, 1H), 3.65 – 3.56 (m, 4H), 3.16 – 3.07 (m, 4H), 2.55 (s, 3H), 1.49 (s, 9H); LCMS (M+H)⁺ m/z 536. (Note: A small peak (4-chloro-pyridin-2-one) in the LC/MS shows m/z 444, 446).

Procedure for the preparation of 3-[6-(4-Amino-piperidin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-iodo-1H-pyridin-2-one and 3-[6-(4-Amino-piperidin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-chloro-1H-pyridin-2-one

25

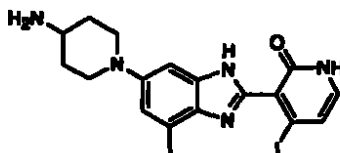


[1-(3-Amino-5-methyl-4-nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester: 5-Fluoro-3-methyl-2-nitro-phenylamine (0.97 g, 5.7 mmol), 4-N-BOC-aminopiperidine (1.60g, 8.0 mmol), diisopropylethylamine (2.5 ml, 14 mmol) and DMSO (10 ml) are combined and stirred at 85°C for 3 hours. The reaction mixture was poured on saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The organic layers were washed with water (3x) and brine, dried over Na₂SO₄ and concentrated. Flash column chromatography on silica (eluent hexanes-ethyl acetate - triethylamine 50-50-1, then 33-66-1) gave the title compound as a yellow solid. (1.57 g, 79%). LCMS (M+H)⁺ m/z 351 (t = 1.55 min.). ¹H NMR (500 MHz, CD₃OD) δ 6.70 (1H, broad s), 6.22 (1H, d, J = 2.5 Hz), 6.13 (1H, d, J = 2.5 Hz), 3.88 (2H, d, J = 13.3 Hz), 3.58 (1H, broad s), 2.98 (2H, t, J = 11.8 Hz), 2.48 (3H, s), 1.92 (2H, d, J = 11.3 Hz), 1.48 (2H, m), 1.45 (9H, s).

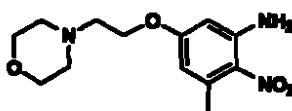


{1-[2-(4-Iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzolimidazol-5-yl]-piperidin-4-yl}-carbamic acid tert-butyl ester: [1-(3-Amino-5-methyl-4-nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (1.54 g, 4.4 mmol) was dissolved in methanol (100 ml). Palladium on carbon (0.3 g, 10% Pd) was added and the suspension stirred vigorously under a balloon pressure of hydrogen overnight. The mixture was filtered through a pad of celite (under argon) into a 3-neck flask, the celite rinsed with methanol and the filtrate cooled to 0°C. A solution of 4-Iodo-2-methoxy-pyridine-3-carbaldehyde (1.21 g, 4.6 mmol) in methanol (50 ml) was added slowly (during 2 hours). The mixture was stirred overnight under air at ambient temperature, then concentrated *in vacuo*. Flash column chromatography on silica (eluent hexanes-ethyl acetate -methanol 5-4-1 gave the title compound. (0.79 g, 32%). LCMS (M+H)⁺ m/z 564 (t = 1.31 min.).

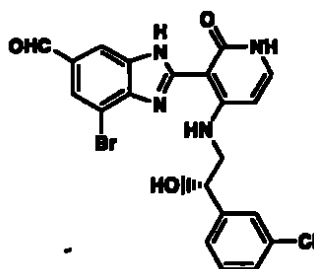
37



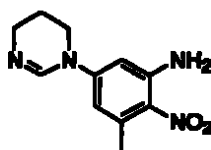
3-[6-(4-Amino-piperidin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-iodo-1H-pyridin-2-one and 3-[6-(4-Amino-piperidin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-chloro-1H-pyridin-2-one : { 1-[2-(4-Iodo-2-methoxy-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl]-piperidin-4-yl }-carbamic acid tert-butyl ester (330 mg, 0.59 mmol) was suspended in 4M HCl in 1,4-dioxane (20 ml) and water (3 ml) was added. (exothermic reaction). The mixture was stirred at ambient temperature overnight, then concentrated *in vacuo* to give an inseparable mixture of the 4-Chloro- and 4-Iodo-
 10 title compounds. The product was used without further purification. LCMS (M+H)⁺ m/z 450 and m/z 358 (both t = 0.69 min.).



15 3-Methyl-5-(2-morpholin-4-ethoxy)-2-nitro-phenylamine: To a solution of 2-morpholin-4-yl-ethanol (5 g, excess) in THF (30 mL) was added NaH (0.21 g, 8.82 mmol) in portion under ice bath. The reaction mixture was stirred at room temperature for 30 min. Then 5-fluoro-3-methyl-2-nitro-phenylamine was added. The reaction mixture was heated to reflux for 6 h, cooled to room temperature, and concentrated.
 20 The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over Na₂SO₄. After concentration, the residue was purified by column chromatography (20% EtOAc / hexane) to yield the title compound (0.70 g, 85%). ¹H NMR (400 MHz, CD₃OD) δ 6.10 (1H, s), 6.09 (1H, s), 4.38 – 4.42 (2H, m), 3.92 – 4.08 (4H, m), 3.72 (1H, d, J = 12 Hz), 3.53 – 3.56 (2H, m), 3.05 – 3.10 (2H, m), 2.48 (3H, s). LCMS (M+H)⁺ m/z 282 (t = 0.73 min.).
 25



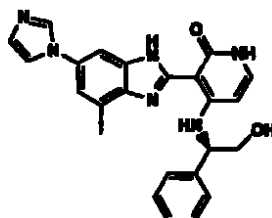
(S)-7-Bromo-2-{4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-3H-benzimidazole-5-carbaldehyde: To a solution of (S)-7-Bromo-2-{4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-3H-benzimidazole-5-carbonitrile (150 mg, 0.31 mmol) in THF (50 mL) was added DIBAL-H (1 M toluene solution, 1.55 mL, 1.55 mmol) at -78°C . The reaction mixture was stirred at -40°C for 10 h and cooled to -78°C . EtOAc (0.5 mL) was added. The reaction mixture was stirred for 30 min at -78°C before water (1 mL) was added. The reaction mixture was warmed to room temperature and concentrated. The residue was passed through a small pad of celite. The filtrate was concentrated and purified by prep. HPLC to give the titled compound (67 mg, 43%). ^1H NMR (400 MHz, CD_3OD) δ 9.45 (1H, s), 7.62 (1H, s), 7.56 (1H, narrow d, $J = 1.6$ Hz), 7.44 (1H, narrow d, $J = 1.0$ Hz), 7.32 - 7.42 (2H, m), 7.24 - 7.30 (3H, m), 6.24 (1H, d, $J = 7.6$ Hz), 5.01 (1H, m), 3.65 - 3.76 (2H, m). LCMS ($\text{M}+\text{H}^+$) m/z 487 ($t = 1.76$ min.).



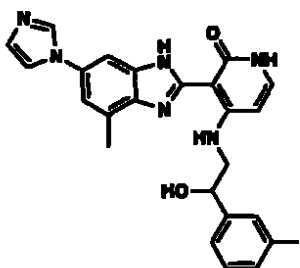
5-(1,4,5,6-Tetrahydropyrimidin-1-yl)-3-methyl-2-nitro aniline: To a stirred solution of 2.0 g (11.76 mmol) of the 5-Flouro-3-methyl-2-nitro aniline in 10 mL of DMSO was added 1.2 g (14.11 mmol) of 1,4,5,6-Tetrahydropyrimidine, and 2.43 g (17.64 mmol) of potassium carbonate, and the mixture was heated at 100°C for 10 hrs, cooled, diluted with water, and extracted with Ethylacetate containing 5% methanol. The combined organic extract was washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent furnished the residue, which was chromatographed (20% of 2M ammonia in methanol and dichloromethane) to produce

1.85 g (67%) of the product as red solid. ^1H NMR (400 MHz, CD_3OD) δ 7.89 (1H, s), 6.53 (1H, d, $J = 2.57$ Hz), 6.44 ((1H, d, $J = 2.1$ Hz), 7.04 (1H, d, $J = 2.1$ Hz), 3.70 (2H, t, $J = 6.0$ Hz), 3.41 (2H, t, $J = 5.65$ Hz), 2.43 (3H, s), 2.05 (2H, m) LCMS ($\text{M}+\text{H}$) $^+$ m/z 235 ($t = 0.78$ min).

5

Example 1 (General procedure for examples 1-21)

- 10 **(S)-4-(2-Hydroxy-1-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:** To a solution of 3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-iodo-1H-pyridin-2-one (30 mg, 0.072 mmol) in DMF (1 mL) were added (S)-(-)-2-phenylglycinol (26 mg, 0.18 mmol) and *N*-methylmorpholine (0.1 mL). The reaction mixture was heated to 80°C for 6 h and
- 15 cooled to room temperature. The solvent was removed under vacuum and the residue was purified by prep. HPLC to yield the title compound (16 mg, 52%). ^1H NMR (300 MHz, CD_3OD) δ 8.07 (1H, narrow t, $J = 1.7$ Hz), 7.76 (2H, s), 7.27 – 7.48 (7H, m), 7.21 (1H, d, $J = 7.5$ Hz), 6.11 (1H, d, $J = 7.5$ Hz), 4.92 (1H, m), 4.03 (1H, dd, $J = 4.5$, 11.2 Hz), 3.95 (1H, dd, $J = 6.2$, 11.2 Hz), 2.75 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 427 ($t =$
- 20 1.44 min.)

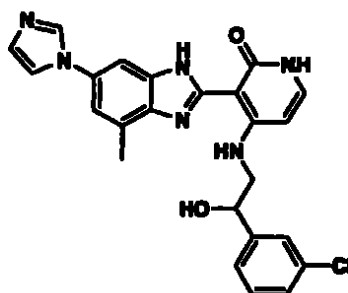
Example 2

25

(±)-4-[2-Hydroxy-2-(3-iodo-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 9.41 (1H, s), 8.06 (1H, s), 7.88 (1H, s), 7.76 (1H, s), 7.71 (1H, s), 7.59 (1H, d, *J* = 7.8 Hz), 7.47 (1H, d, *J* = 7.8 Hz) 7.32 (1H, s) 7.29 (1H, d, *J* = 7.6 Hz) 7.09 (1H, t, *J* = 7.8 Hz), (6.24
5 (1H, d, *J* = 7.6 Hz), 4.97 (1H, dd, *J* = 5.0, 6.0 Hz), 3.75 (1H, dd, *J* = 5.0, 13.5 Hz), 3.67 (1H, dd, *J* = 6.0, 13.5 Hz), 2.68 (3H, s). LCMS (M+H)⁺ *m/z* 553 (*t* = 1.43 min.).

Example 3

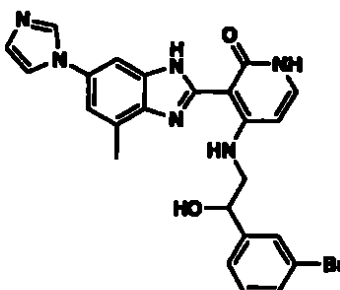
10



(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 9.39 (1H, narrow t, *J* = 1.4 Hz), 8.04 (1H, narrow t, *J* = 1.7 Hz), 7.76 (1H, narrow t, *J* = 1.7
15 Hz), 7.69 (1H, narrow d, *J* = 1.9 Hz), 7.55 (1H, s), 7.23 – 7.42 (5H, m), 6.25 (1H, d, *J* = 7.6 Hz), 5.01 (1H, dd, *J* = 4.8, 6.4 Hz), 3.76 (1H, dd, *J* = 4.8, 13.4 Hz), 3.66 (1H, dd, *J* = 6.4, 13.4 Hz), 2.67 (3H, s). LCMS (M+H)⁺ *m/z* 461 (*t* = 1.46 min.).

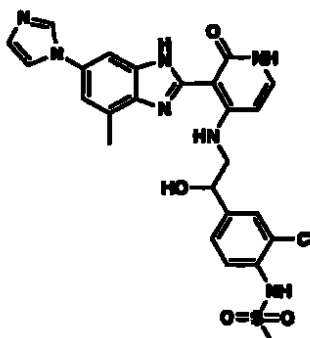
Example 4

20



39

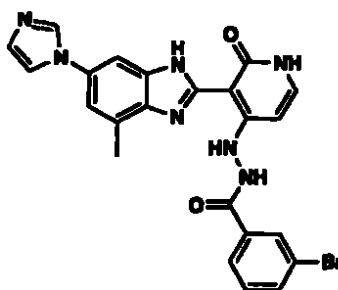
(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 9.38 (1H, s), 8.02 (1H, s), 7.74 (1H, s), 7.69 (1H, s), 7.66 (1H, narrow d, *J* = 1.4 Hz), 7.20 – 7.48 (5H, m), 6.21 (1H, d, *J* = 7.6 Hz), 4.99 (1H, dd, *J* = 4.8, 6.3 Hz), 3.73 (1H, dd, *J* = 4.8, 13.5 Hz), 3.64 (1H, dd, *J* = 6.3, 13.5 Hz), 2.65 (3H, s). LCMS (M+H)⁺ *m/z* 505 (*t* = 1.47 min.).

Example 5

10

(±)-N-(2-Chloro-4-{1-hydroxy-2-[3-(6-imidazol-1-yl)-4-methyl-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-phenyl)-methanesulfonamide: ¹H NMR (300 MHz, CD₃OD) δ 9.39 (1H, s), 8.05 (1H, s), 7.76 (1H, s), 7.68 (1H, s), 7.62 (1H, narrow d, *J* = 1.5 Hz), 7.52 (1H, s), 7.42 – 7.49 (2H, m), 7.31 (1H, s), 7.30 (1H, d, *J* = 7.6 Hz), 6.26 (1H, d, *J* = 7.6 Hz), 5.01 (1H, dd, *J* = 5.0, 5.6 Hz), 3.76 (1H, d, *J* = 5.0, 13.4 Hz), 3.74 (1H, dd, *J* = 5.6, 13.4 Hz), 2.98 (3H, s), 2.68 (3H, s). LCMS (M+H)⁺ *m/z* 554 (*t* = 1.11 min.).

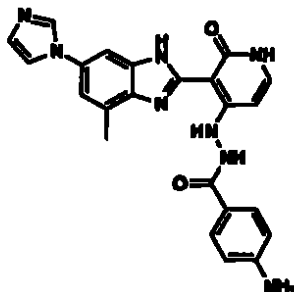
15

Example 6

20

3-Bromo-benzoic-acid *N'*-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-yl]-hydrazide: ¹H NMR (300 MHz, CD₃OD) δ 9.40 (1H, narrow t, *J* = 1.4 Hz), 8.14 (1H, narrow t, *J* = 1.7 Hz), 8.05 (1H, narrow t, *J* = 1.7 Hz), 7.95 (1H, d, *J* = 7.9 Hz), 7.81 (1H, d, *J* = 7.9 Hz), 7.74 – 7.77 (2H, m), 7.49 (1H, t, *J* = 7.9 Hz), 7.41 (1H, d, *J* = 7.4 Hz), 7.34 (1H, s), 6.38 (1H, d, *J* = 7.4 Hz), 2.70 (3H, s). LCMS (M+H)⁺ *m/z* 504 (*t* = 1.44 min.).

Example 7

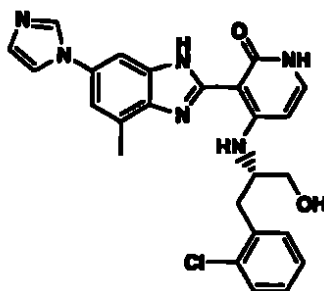


10

4-Amino-benzoic-acid *N'*-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-yl]-hydrazide: ¹H NMR (300 MHz, CD₃OD) δ 9.41 (1H, s), 8.06 (1H, s), 7.76 – 7.79 (4H, m), 7.39 (1H, d, *J* = 7.4 Hz), 7.36 (1H, s), 6.81 (2H, d, *J* = 8.6 Hz), 6.36 (1H, d, *J* = 7.4 Hz), 2.70 (3H, s). LCMS (M+H)⁺ *m/z* 441 (*t* = 0.96 min.).

15

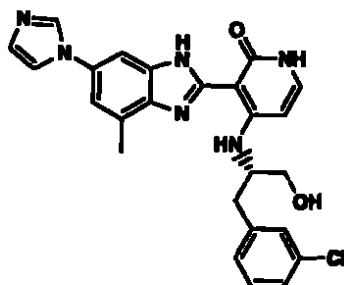
Example 8



(S)-4-[2-(2-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 9.41 (1H, s), 8.05 (1H, narrow t, *J* = 1.7 Hz), 7.76 (1H, narrow t, *J* = 1.7 Hz), 7.72 (1H, narrow d, *J* = 1.9 Hz), 7.08 – 7.36 (6H, m), 6.10 (1H, d, *J* = 7.7 Hz), 3.98 – 4.24

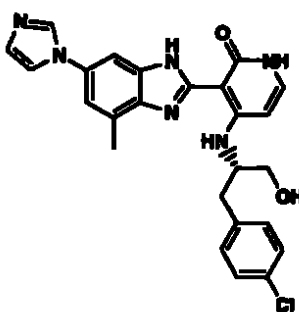
(1H, m), 3.84 (1H, dd, $J = 4.4, 11.2$ Hz), 3.79 (1H, dd, $J = 4.8, 11.2$ Hz), 3.35 (1H, dd, $J = 5.4, 13.6$ Hz), 3.09 (1H, dd, $J = 7.8, 13.6$ Hz), 2.72 (3H, s). LCMS (M+H)⁺ m/z 475 ($t = 1.56$ min.).

5 Example 9

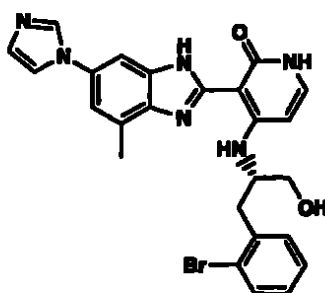


(S)-4-[2-(3-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 9.42 (1H, s), 8.07 (1H, narrow t, $J = 1.7$ Hz), 7.75 – 7.78 (2H, m), 7.14 – 7.37 (6H, m), 6.18 (1H, d, $J = 7.7$ Hz), 4.07 – 4.11 (1H, m), 3.76 – 3.77 (2H, m), 3.17 (1H, dd, $J = 5.1, 13.7$ Hz), 2.98 (1H, dd, $J = 8.2, 13.7$ Hz), 2.71 (3H, s). LCMS (M+H)⁺ m/z 475 ($t = 1.57$ min.).

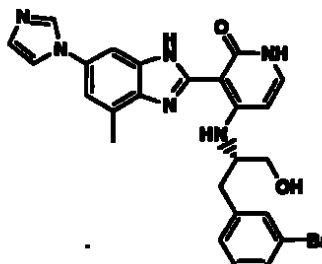
15 Example 10



(S)-4-[2-(4-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 9.42 (1H, s), 8.07 (1H, narrow t, $J = 1.6$ Hz), 7.77 (1H, narrow t, $J = 1.6$ Hz), 7.73 (1H, narrow d, $J = 1.9$ Hz), 7.16 – 7.37 (6H, m), 6.19 (1H, d, $J = 7.7$ Hz), 4.06 – 4.10 (1H, m), 3.72 – 3.77 (2H, m), 3.14 (1H, dd, $J = 5.3, 13.8$ Hz), 2.98 (1H, dd, $J = 7.8, 13.8$ Hz), 2.69 (3H, s). LCMS (M+H)⁺ m/z 475 ($t = 1.61$ min.).

Example 11

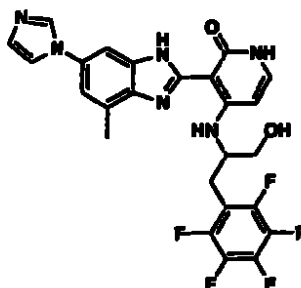
- 5 **(S)-4-[2-(2-Bromo-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 9.41 (1H, s), 8.06 (1H, s), 7.75 – 7.77 (2H, m), 7.52 (1H, dd, $J = 1.5, 7.5$ Hz), 7.36 (1H, d, $J = 1.9$ Hz), 7.34 (1H, s), 7.03 – 7.16 (3H, m), 6.09 (1H, d, $J = 7.7$ Hz), 4.15 – 4.27 (1H, m), 3.82 (2H, m), 3.35 (1H, dd, $J = 5.0, 13.6$ Hz), 3.10 (1H, dd, $J = 9.0,$
- 10 13.6 Hz), 2.74 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 519 ($t = 1.56$ min.).

Example 12

- 15 **(S)-4-[2-(3-Bromo-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 9.41 (1H, s), 8.06 (1H, s), 7.74 – 7.77 (2H, m), 7.47 (1H, s), 7.24 – 7.31 (4H, m), 7.11 (1H, d, $J = 7.7$ Hz), 6.16 (1H, d, $J = 7.7$ Hz), 4.05 – 4.11 (1H, m), 3.76 (2H, m), 3.15 (1H, dd, $J = 5.0, 13.6$ Hz), 2.96 (1H, dd, $J = 8.3, 13.6$ Hz), 2.70 (3H, s). LCMS
- 20 $(\text{M}+\text{H})^+$ m/z 519 ($t = 1.54$ min.).

41

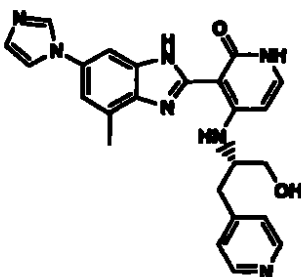
Example 13



5 **(+)-4-(1-Hydroxymethyl-2-pentafluorophenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 9.40 (1H, s), 8.06 (1H, narrow t, $J = 1.8$ Hz), 7.77 (1H, narrow t, $J = 1.7$ Hz), 7.74 (1H, narrow d, $J = 1.8$ Hz), 7.35 (1H, s), 7.29 (1H, d, $J = 7.6$ Hz), 6.22 (1H, d, $J = 7.6$ Hz), 4.24 (1H, m), 3.82 (2H, dd, $J = 2.6, 4.5$ Hz), 3.23 (2H, t, $J = 6.5$ Hz), 2.70 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 531 ($t = 1.61$ min.).

10

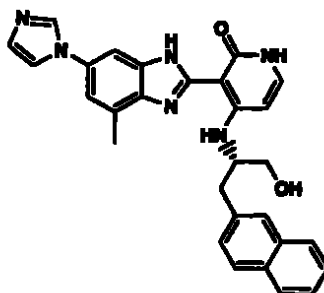
Example 14



15 **(S)-4-(1-Hydroxymethyl-2-pyridin-4-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:** ^1H NMR (400 MHz, CD_3OD) δ 9.42 (1H, s), 8.67 (2H, d, $J = 6.6$ Hz), 8.07 (2H, d, $J = 6.6$ Hz), 8.06 (1H, s), 7.77 (2H, s), 7.36 (1H, s), 7.28 (1H, d, $J = 7.6$ Hz), 6.24 (1H, d, $J = 7.6$ Hz), 4.35 (1H, m), 3.82 (2H, d, $J = 4.4$ Hz), 3.50 (1H, dd, $J = 4.4, 13.6$ Hz), 3.40 (1H, dd, $J = 8.7, 13.6$ Hz), 2.71 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 442 ($t = 0.96$ min.).

20

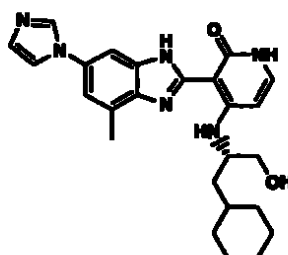
Example 15



5 **(S)-4-(1-Hydroxymethyl-2-naphthalen-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 7.99 (1H, narrow t, $J = 1.7$ Hz), 7.26 – 7.75 (11H, m), 7.15 (1H, d, $J = 7.6$ Hz), 6.19 (1H, d, $J = 7.6$ Hz), 4.16 – 4.20 (1H, m), 3.75 – 3.86 (2H, m), 3.30 (1H, dd, $J = 5.4$, 13.6 Hz), 3.15 (1H, dd, $J = 7.6$, 13.6 Hz), 2.60 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 491 ($t = 1.71$ min.).

10

Example 16

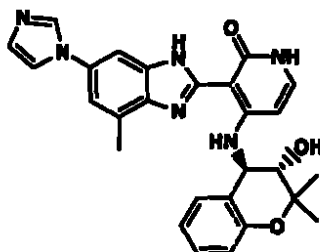


15 **(S)-4-(2-Cyclohexyl-1-hydroxymethyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 9.40 (1H, s), 8.06 (1H, narrow t, $J = 1.7$ Hz), 7.76 (1H, narrow t, $J = 1.7$ Hz), 7.73 (1H, narrow d, $J = 1.7$ Hz), 7.34 (1H, d, $J = 7.6$ Hz), 7.33 (1H, s), 6.34 (1H, d, $J = 7.6$ Hz), 3.89 – 3.94 (1H, m), 3.68 (2H, d, $J = 4.9$ Hz), 2.68 (3H, s), 1.62 – 1.83 (7H, m), 0.95 – 1.26 (6H, m). LCMS $(\text{M}+\text{H})^+$ m/z 447 ($t = 1.71$ min.).

20

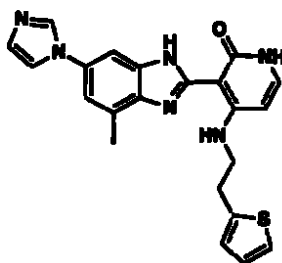
42

Example 17

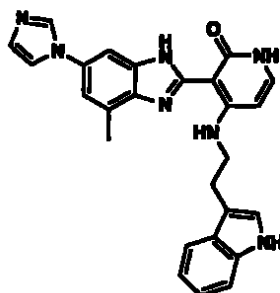


(3S,4R)-4-(3-Hydroxy-2,2-dimethyl-chroman-4-ylamino)-3-(6-imidazol-1-yl-4-
 5 methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (300 MHz, CD_3OD) δ
 9.36 (1H, s), 8.02 (1H, narrow t, $J = 1.7$ Hz), 7.73 (1H, narrow t, $J = 1.7$ Hz), 7.69
 (1H, narrow d, $J = 2.0$ Hz), 7.37 (1H, d, $J = 7.6$ Hz), 7.18 – 7.30 (3H, m), 6.89 (1H, t,
 $J = 7.6$ Hz), 6.85 (1H, d, $J = 8.4$ Hz), 6.61 (1H, d, $J = 7.6$ Hz), 4.93 (1H, d, $J = 8.2$
 Hz), 3.80 (1H, d, $J = 8.2$ Hz), 2.46 (3H, s), 1.48 (3H, s), 1.35 (3H, s). LCMS ($\text{M}+\text{H}$)⁺
 10 m/z 483 ($t = 1.70$ min.).

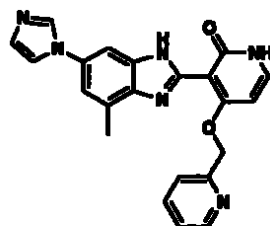
Example 18



15 3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-thiophen-2-yl-
 ethylamino)-1H-pyridin-2-one: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 13.17 (1H, broad
 s), 11.32 (1H, broad s), 11.03 (1H, broad s), 9.59 (1H, broad s), 8.22 (1H, broad s),
 7.91 (1H, s), 7.82 (1H, d, $J = 2.0$ Hz), 7.41 (1H, t, $J = 6.9$ Hz), 7.36 (1H, dd, $J = 1.0$,
 5.1 Hz), 7.30 – 7.40 (1H, m), 7.05 (1H, broad s), 7.01 (1H, t, $J = 4.2$ Hz), 6.23 (1H, d,
 20 $J = 7.5$ Hz), 3.74 (2H, t, $J = 6.5$ Hz), 3.25 (2H, t, $J = 6.5$ Hz), 2.58 (3H, s).

Example 19

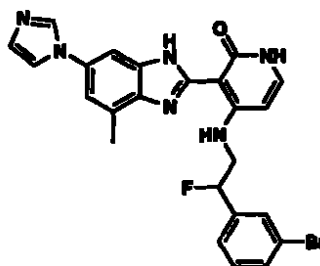
3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(1H-Indol-3-yl)-
ethylamino]-1H-pyridin-2-one: ¹H NMR (500 MHz, DMSO-d₆) δ 13.17 (1H, broad
 s), 11.27 (broad s, 1H), 11.00 (1H, broad s), 10.89 (1H, s), 9.58 (1H, broad s), 8.30
 (1H, broad s), 7.91 (1H, s), 7.80 (1H, s), 7.63 (1H, d, *J* = 7.9 Hz), 7.40 (1H, t, *J* = 6.9
 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.30 – 7.40 (2H, m), 7.07 (1H, t, *J* = 7.5 Hz), 6.99 (1H,
 t, *J* = 7.6 Hz), 6.23 (1H, dd, *J* = 0.8, 7.2 Hz), 3.76 (2H, broad s), 3.17 (2H, t, *J* = 6.7
 Hz), 2.50 (3H, s).

Example 20

3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(pyridin-2-ylmethoxy)-1H-
pyridin-2-one: To a solution of 3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-
 4-iodo-1H-pyridin-2-one (25 mg, 0.06 mmol) in DMF (2 mL) were added pyridine
 carbinol (26 mg, 0.24 mmol) and cesium fluoride (36 mg, 0.24 mmol). The reaction
 mixture was heated to 130°C for 14 h and cooled to room temperature. After
 concentration *in vacuo*, the residue was purified by prep. HPLC to yield the title
 compound (8.2 mg, 34%). ¹H NMR (300 MHz, CD₃OD) δ 9.58 (1H, narrow d, *J* = 1.2
 Hz), 8.92 (1H, d, *J* = 4.9 Hz), 8.19 (1H, narrow t, *J* = 1.2 Hz), 8.12 (1H, s), 7.97 –
 8.02 (2H, m), 7.85 (1H, narrow t, *J* = 1.8 Hz), 7.81 (1H, narrow t, *J* = 1.0 Hz), 7.63

(1H, d, $J = 7.9$ Hz), 7.54 (1H, t, $J = 6.2$ Hz), 6.81 (1H, $J = 7.5$ Hz), 5.86 (2H, s), 2.86 (3H, s). LCMS (M+H)⁺ m/z 399 ($t = 1.07$ min.).

Example 21

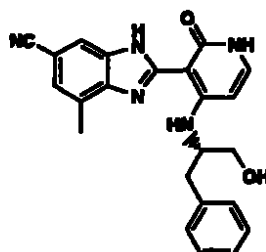


5

(±)-4-[2-(3-Bromo-phenyl)-2-fluoro-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 9.40 (1H, t, $J = 1.4$ Hz), 8.06 (1H, t, $J = 1.9$ Hz), 7.76 (1H, t, $J = 1.7$ Hz), 7.72 (1H, d, $J = 1.9$ Hz), 7.66 (1H, s), 7.27 – 7.50 (5H, m), 6.29 (1H, d, $J = 7.6$ Hz), 5.75 – 5.94 (1H, m), 3.86 – 4.06 (2H, m), 2.64 (3H, s). LCMS (M+H)⁺ m/z 507 ($t = 1.70$ min.).

10

Example 22 (General procedure for examples 22-28)



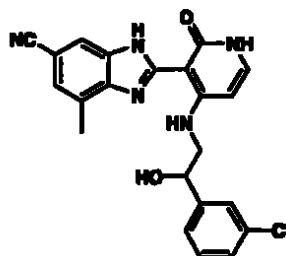
15

(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile: To a solution of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazole-5-carbonitrile (0.7 g, 2.19 mmol) in DMF (15 mL) were added *N*-methylmorpholine (0.66 g, 6.57 mmol) and (S)-(-)-2-amino-3-phenyl-1-propanol (0.40 g, 2.63 mmol). The reaction mixture was heated to 80°C for 6 h and then cooled to room temperature. After concentration *in vacuo*, the residue was purified by flash chromatography (3% MeOH / CH₂Cl₂) to yield the title compound (0.59 g, 68%) as a yellow foam. ¹H NMR (400 MHz, CD₃OD) δ 7.74 (1H, s), 7.63 (1H, s), 7.12 – 7.27 (6H, m), 6.07 (1H, d, $J = 7.5$ Hz),

20

3.97 (1H, m), 3.74 (2H, t, $J = 5$ Hz), 3.14 (1H, dd, $J = 5.5, 14.0$ Hz), 2.94 (1H, dd, $J = 7.9, 14.0$ Hz), 2.60 (3H, s). LCMS (M+H)⁺ m/z 400 ($t = 1.71$ min.).

Example 23

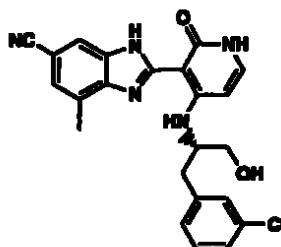


5

(±)-2-(4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazole-5-carbonitrile: ¹H NMR (300 MHz, DMSO-d₆) δ 7.92 (1H, s), 7.59 (1H, s), 7.28 – 7.47 (5H, m), 6.19 (1H, d, $J = 7.3$ Hz), 4.92 – 4.96 (1H, m), 3.53 – 3.73 (2H, m), 2.58 (3H, s). LCMS (M+H)⁺ m/z 420 ($t = 1.99$ min.).

10

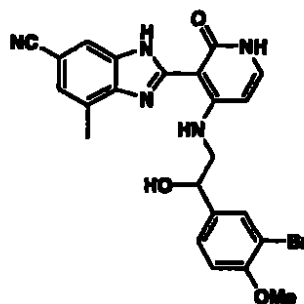
Example 24



(S)-2-(4-[2-(3-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazole-5-carbonitrile: ¹H NMR (400 MHz, CD₃OD) δ 7.86 (1H, s), 7.10 – 7.33 (6H, m), 6.12 (1H, d, $J = 7.6$ Hz), 4.01 – 4.05 (1H, m), 3.75 (2H, d, $J = 4.9$ Hz), 3.15 (1H, dd, $J = 4.9, 13.5$ Hz), 2.86 – 3.00 (1H, m), 2.63 (3H, s). LCMS (M+H)⁺ m/z 434 ($t = 1.81$ min.).

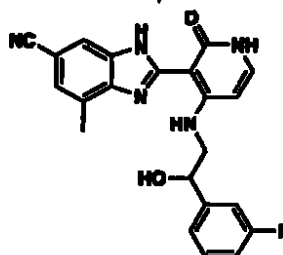
20

Example 25



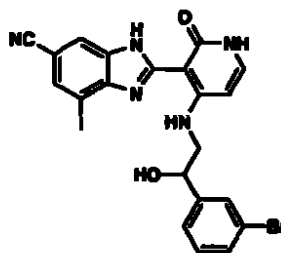
(±)-2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carbonitrile: ^1H NMR (300 MHz, CD_3OD) δ 7.86 (1H, s), 7.75 (1H, s), 7.67 (1H, s), 7.28 – 7.40 (2H, m), 6.95 (1H, d, $J = 8.5$ Hz), 6.24 (1H, d, $J = 7.4$ Hz), 4.93 (1H, m), 3.65 – 3.97 (2H, m), 3.82 (3H, s), 2.57 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 494 ($t = 2.10$ min.).

10 Example 26



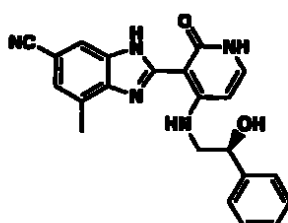
(±)-2-{4-[2-(3-Fluoro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carbonitrile: ^1H NMR (400 MHz, CD_3OD) δ 7.70 (1H, s), 7.49 (1H, s), 7.22 – 7.32 (4H, m), 6.92 (1H, d, $J = 8.9$ Hz), 6.17 (1H, d, $J = 7.2$ Hz), 4.92 (1H, t, $J = 6.3$ Hz), 3.66 (2H, d, $J = 5.9$ Hz), 2.56 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 404 ($t = 1.65$ min.).

Example 27



(±)-2-[4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile: ¹H NMR (300 MHz, CD₃OD) δ 7.92 (1H, s), 7.72 (1H, s), 7.26 – 7.50 (5H, m), 6.19 (1H, d, *J* = 7.1 Hz), 4.93 (1H, t, *J* = 4.3 Hz), 3.47 – 3.73 (2H, m), 2.58 (3H, s). LCMS (M+H)⁺ *m/z* 464 (*t* = 2.00 min.).

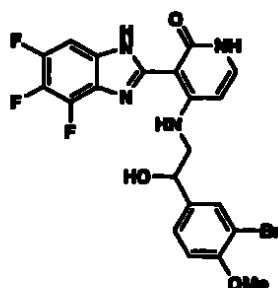
Example 28



10 (S)-2-[4-(2-Hydroxy-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile: ¹H NMR (400 MHz, CD₃OD) δ 8.04 (1H, s), 7.74 (1H, s), 7.24 – 7.51 (6H, m), 6.22 (1H, d, *J* = 7.5 Hz), 5.00 (1H, m), 3.64 – 3.74 (2H, m), 2.60 (3H, s). LCMS (M+H)⁺ *m/z* 386 (*t* = 1.65 min.).

15 Examples 29-35 were prepared from commercially or readily available diamines which were prepared and condensed with 4-iodo-2-methoxy-pyridine-3-carbaldehyde as described in Scheme III.

Example 29

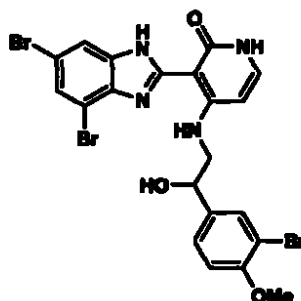


20

(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4,5,6-trifluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃COCD₃) δ 13.26 (1H, broad s), 10.93 (1H, broad s), 10.27 (1H, broad s), 7.76 (1H, s), 7.54 –

7.56 (2H, m), 7.41 – 7.42 (1H, m), 7.06 (1H, d, $J = 8.2$ Hz), 6.29 (1H, d, $J = 7.5$ Hz), 5.05 – 5.07 (1H, m), 3.87 (3H, s), 3.74 – 3.79 (1H, m), 3.65 – 3.69 (1H, m).

Example 30

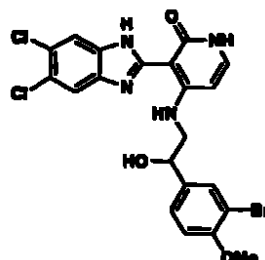


5

(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4,6-dibromo-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (500 MHz, CD_3COCD_3) δ 13.18 (1H, broad s), 11.18 (1H, broad s), 10.20 (1H, broad s), 7.92 (1H, s), 7.78 (1H, s), 7.52 – 7.55 (3H, m), 7.03 (1H, d, $J = 8.5$ Hz), 6.28 (1H, d, $J = 7.4$ Hz), 5.06 – 5.08 (1H, m), 3.86 (3H, s), 3.73 – 3.77 (1H, m), 3.66 – 3.70 (1H, m).

10

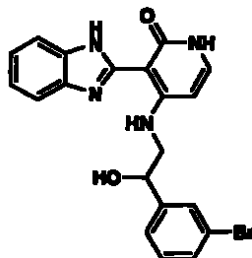
Example 31



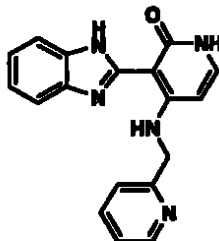
15

(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(5,6-dichloro-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (500 MHz, CD_3COCD_3) δ 7.79 (3H, m), 7.53 (1H, dd, $J = 2.0, 8.4$ Hz), 7.41 – 7.44 (1H, m), 7.08 (1H, d, $J = 8.4$ Hz), 6.29 (1H, d, $J = 7.5$ Hz), 5.05 – 5.08 (1H, m), 3.89 (3H, s), 3.74 – 3.78 (1H, m), 3.70 – 3.72 (1H, m).

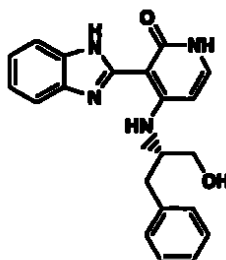
20

Example 32

(±)-3-(1H-Benzimidazol-2-yl)-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃COCD₃) δ 7.80 (1H, s), 7.64 – 7.69 (2H, m), 7.60 (1H, d, *J* = 7.7 Hz), 7.46 – 7.48 (2H, m), 7.33 (1H, t, *J* = 7.8 Hz), 7.19 – 7.22 (2H, m), 6.59 (1H, d, *J* = 4.5 Hz), 5.12 – 5.14 (1H, m), 5.13 (1H, dd, *J* = 4.5, 7.2 Hz), 3.82 (1H, dd, *J* = 4.5, 13.6 Hz), 3.71 (1H, dd, *J* = 7.2, 13.6 Hz).

Example 33

3-(1H-Benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃COCD₃) δ 8.96 – 8.98 (1H, m), 8.46 – 8.49 (1H, m), 8.03 (1H, d, *J* = 8.0 Hz), 7.93 (1H, t, *J* = 6.4 Hz), 7.69 – 7.73 (2H, m), 7.53 (1H, d, *J* = 7.5 Hz), 7.28 – 7.32 (2H, s), 6.34 (1H, d, *J* = 7.5 Hz), 5.29 (2H, m).

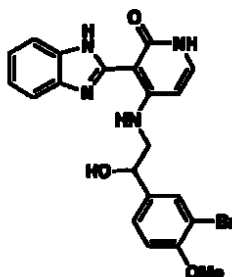
Example 34

46

(S)-3-(1H-Benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃COCD₃) δ 7.67 – 7.69 (2H, m), 7.15 – 7.44 (8H, m), 6.31 (1H, d, *J* = 7.5 Hz), 4.10 – 4.13 (1H, m), 3.76 – 3.82 (2H, m), 3.23 (1H, dd, *J* = 5.6, 13.7 Hz), 3.04 (1H, dd, *J* = 8.1, 13.7 Hz).

5

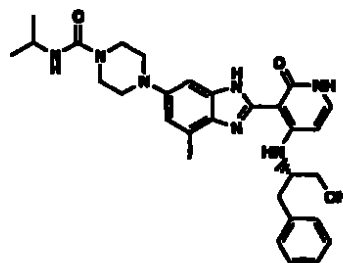
Example 35



(±)-3-(1H-Benzimidazol-2-yl)-4-[2-(3-bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃COCD₃) δ 7.78 (1H, s), 7.68 (2H, s), 7.50 – 7.55 (2H, m), 7.21 – 7.24 (2H, m), 7.06 (1H, d, *J* = 8.4 Hz), 6.44 (1H, d, *J* = 7.5 Hz), 5.08 (1H, dd, *J* = 4.6, 7.2 Hz), 3.87 (3H, s), 3.79 (1H, dd, *J* = 4.6, 13.4 Hz), 3.71 (1H, dd, *J* = 7.2, 13.4 Hz).

15 Examples 36 - 43 were prepared according to Scheme V.

Example 36 (General procedure for examples 36-43)

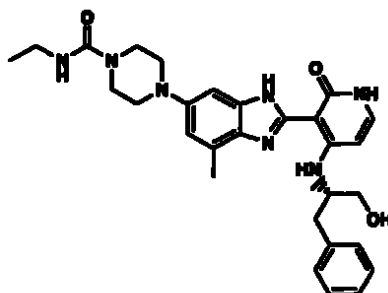


20

(S)-4-{2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl}-piperazine-1-carboxylic acid isopropylamide: To a solution of (S)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (30 mg, 0.063

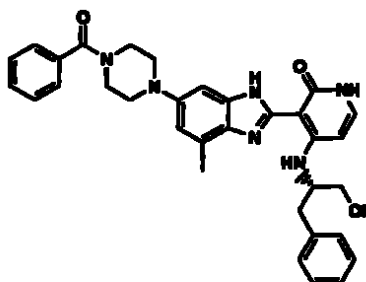
mmol) in methanol (2 mL) was added *isopropyl isocyanate* (2 drops). The reaction mixture was stirred at room temperature for 5 min. Concentration gave the residue, which was purified by prep. HPLC to yield the title compound (23.8 mg, 69%). ¹H NMR (400 MHz, CD₃OD) δ 7.55 (1H, s), 7.14 – 7.28 (7H, m), 6.12 (1H, d, *J* = 7.8 Hz), 4.01 – 4.03 (1H, m), 3.92 (quintet, *J* = 6.6 Hz), 3.80 (4H, m), 3.76 (1H, dd, *J* = 4.8, 11.2 Hz), 3.70 (1H, dd, *J* = 5.2, 11.2 Hz), 3.61 – 3.64 (4H, m), 3.09 (1H, dd, *J* = 5.6, 13.7 Hz), 2.91 (1H, dd, *J* = 8.0, 13.7 Hz), 2.64 (3H, s), 1.19 (6H, d, *J* = 6.8 Hz). LCMS (M+H)⁺ *m/z* 545 (*t* = 1.99 min.).

10 Example 37



(*S*)-4-{2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl}-piperazine-1-carboxylic acid ethylamide: ¹H NMR (400 MHz, CD₃OD) δ 7.55 (1H, s), 7.12 – 7.28 (7H, m), 6.12 (1H, d, *J* = 7.8 Hz), 4.01 – 4.05 (1H, m), 3.62 – 3.81 (10H, m), 3.24 (2H, q, *J* = 7.2 Hz), 3.08 (1H, dd, *J* = 5.6, 13.7 Hz), 2.91 (1H, dd, *J* = 8.0, 13.7 Hz), 2.65 (3H, s), 1.14 (3H, t, *J* = 7.2 Hz). LCMS (M+H)⁺ *m/z* 531 (*t* = 1.93 min.).

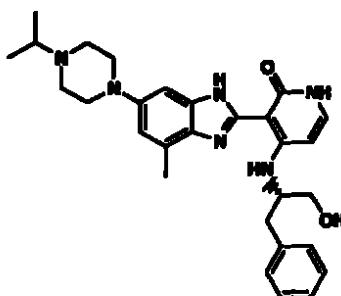
20 Example 38



47

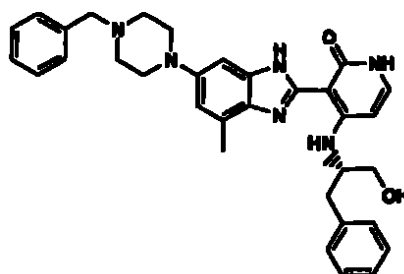
(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-[4-(1-phenyl-methanoyl)-piperazin-1-yl]-1H-benzimidazol-2-yl]-1H-pyridin-2-one: To a solution of (S)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (30 mg, 0.063 mmol) in methanol (2 mL) was added benzoyl chloride (1 drop). The reaction mixture was stirred for 5 min. and concentrated. The residue was purified by prep. HPLC to yield the title compound (11 mg, 33%). ¹H NMR (400 MHz, CD₃OD) δ 7.48 – 7.54 (5H, m), 7.37 (1H, s), 7.13 – 7.26 (7H, m), 6.08 (1H, d, *J* = 7.7 Hz), 3.79 – 4.02 (5H, m), 3.76 (1H, dd, *J* = 4.7, 11.2 Hz), 3.67 (1H, dd, *J* = 5.7, 11.2 Hz), 3.54 (4H, m), 3.03 (1H, dd, *J* = 5.7, 13.7 Hz), 2.89 (1H, dd, *J* = 8.0, 13.7 Hz), 2.62 (3H, s). LCMS (M+H)⁺ *m/z* 563 (*t* = 2.19 min.).

Example 39

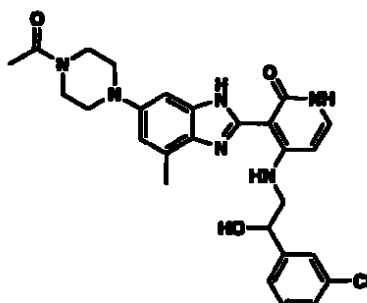


(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[6-(4-isopropyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: To a solution of (S)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (25 mg, 0.054 mmol) in methanol (0.5 mL) was added acetone (0.25 mL) and 1 M THF solution of NaCNBH₃ (0.2 mL). The reaction mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was purified by prep. HPLC to yield the title compound (12 mg, 44%). ¹H NMR (400 MHz, CD₃OD) δ 7.10 – 7.24 (6H, m), 7.08 (1H, s), 7.06 (1H, s), 6.06 (1H, d, *J* = 7.9 Hz), 3.58 – 4.01 (10H, m), 3.34 (1H, m), 3.14 (1H, m), 2.98 (1H, dd, *J* = 5.9, 13.7 Hz), 2.83 (1H, dd, *J* = 7.9, 13.7 Hz), 2.60 (3H, s), 1.44 (6H, d, *J* = 6.7 Hz). LCMS (M+H)⁺ *m/z* 501 (*t* = 1.80 min.).

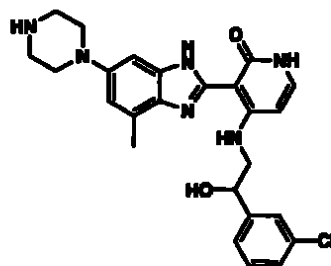
25

Example 40

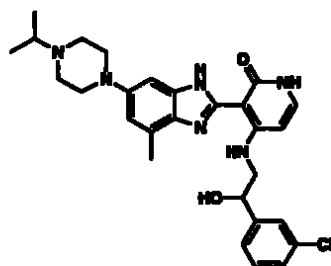
- (S)-3-[6-(4-Benzyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one:** ^1H NMR (400 MHz, CD_3OD) δ 7.50 – 7.57 (6H, m), 7.04 – 7.27 (7H, m), 6.07 (1H, d, $J = 7.8$ Hz), 4.22 (2H, s), 3.97 – 4.00 (1H, m), 3.34 – 3.77 (2H, m), 2.82 – 3.04 (10H, m), 2.58 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 549 ($t = 1.93$ min.).

Example 41

- (±)-3-[6-(4-Acetyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-chlorophenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one:** ^1H NMR (400 MHz, CD_3OD) δ 7.50 (1H, s), 7.25 – 7.49 (5H, m), 7.20 (1H, s), 6.25 (1H, d, $J = 8.0$ Hz), 4.94 (1H, dd, $J = 4.6, 7.1$ Hz), 3.88 – 3.92 (4H, m), 3.50 – 3.65 (6H, m), 2.62 (3H, s), 2.20 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 521 ($t = 2.13$ min.).

Example 42

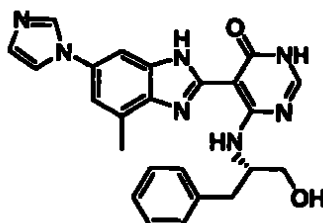
(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (400 MHz, CD_3OD) δ 7.47 (1H, s), 7.25 – 7.38 (4H, m), 7.07 (2H, s), 6.25 (1H, d, $J = 7.6$ Hz), 4.90 (1H, m), 3.42 – 3.66 (10 H, m), 2.59 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 479 ($t = 1.90$ min.).

Example 43

10

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4-isopropyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ^1H NMR (400 MHz, CD_3OD) δ 7.47 (1H, s), 7.25 – 7.38 (4H, m), 7.06 (2H, s), 6.26 (1H, d, $J = 7.6$ Hz), 4.91 – 4.93 (1H, m), 3.89 – 3.92 (2H, m), 3.51 – 3.64 (5H, m), 3.31 – 3.37 (2H, m), 3.09 – 3.30 (2H, m), 2.59 (3H, s), 1.44 (6H, d, $J = 6.6$ Hz). LCMS ($\text{M}+\text{H}$) $^+$ m/z 521 ($t = 1.95$ min.).

15

Example 44

20

(S)-6-(1-Hydroxymethyl-2-phenyl-ethylamino)-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one:

(S)-2-[6-Chloro-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-pyrimidin-4-ylamino]-3-phenyl-propan-1-ol: To a solution of 2-(4,6-dichloro-pyrimidin-5-yl)-6-imidazol-1-yl-4-methyl-1H-benzimidazole (40 mg, 0.16 mmol) in *isopropanol* (5 mL) was added (S)-(-)-2-amino-3-phenyl-propanol (35 mg, 0.23 mmol) and triethylamine (0.5 mL). The reaction mixture was heated to 80°C for 4 h, cooled to room temperature and concentrated with high vacuum. The crude product was used for the next step without purification. LCMS (M+H)⁺ m/z 460 (t = 2.13 min.).

(S)-6-(1-Hydroxymethyl-2-phenyl-ethylamino)-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one: To a solution of (S)-2-[6-chloro-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-pyrimidin-4-ylamino]-3-phenyl-propan-1-ol in 4 N HCl (0.5 mL) and acetic acid (0.5 mL) was added two drops of water. The reaction mixture was heated to 100°C for 8 h, cooled to room temperature, and neutralized with ammonia in methanol. After concentration, the residue was purified by prep. HPLC to yield the title compound (26 mg, 37% for two steps). ¹H NMR (400 MHz, CD₃OD) δ 9.41 (1H, narrow t, J = 1.5 Hz), 8.06 (1H, narrow dd, J = 1.6, 1.9 Hz), 7.93 (1H, s), 7.77 (1H, narrow dd, J = 1.6, 1.8 Hz), 7.73 (1H, narrow d, J = 1.9 Hz), 7.11 – 7.21 (6H, m), 4.70 – 4.74 (1H, m), 3.74 (2H, d, J = 4.7 Hz), 3.11 (1H, dd, J = 6.1, 13.5 Hz), 3.00 (1H, dd, J = 7.8, 13.5 Hz), 2.70 (3H, s). LCMS (M+H)⁺ m/z 442 (t = 2.17 min.).

Examples 45 - 383 were prepared according to the general methods described above (Scheme III)

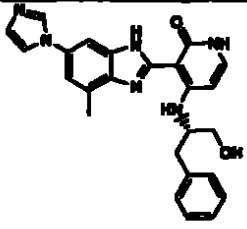
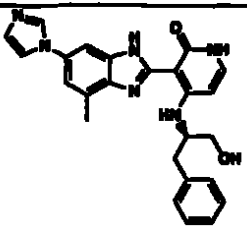
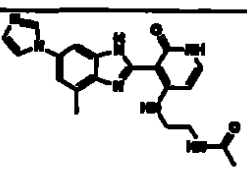
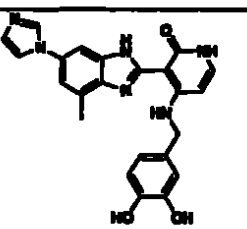
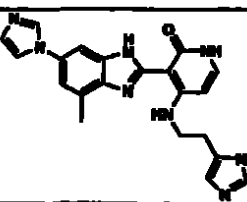
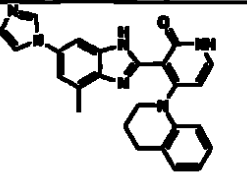
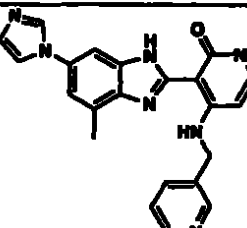
LCMS conditions:

- a) YMC C18 S5 4.6 x 50 mm; 0 – 100% gradient over 4 min*; 4 mL/min flow rate
- b) YMC ODS-A C18 S7 3.0 x 50 mm; 0 – 100% gradient over 2 min*; 5 mL/min flow rate
- c) YMC C18 S5 4.5 x 50 mm; 0 – 100% gradient over 8 min*; 2.5 mL/min flow rate

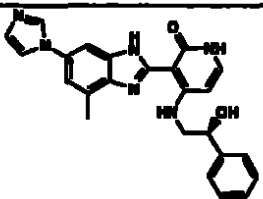
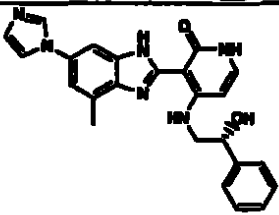
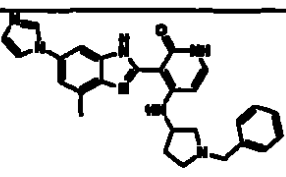
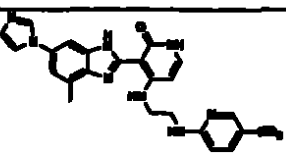
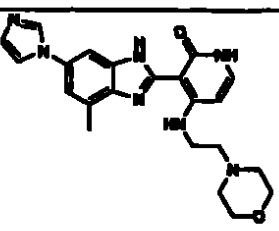
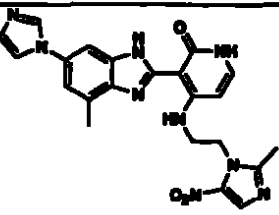
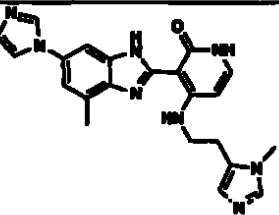
- d) YMC C18 S7 3.0 x 50 mm; 0 – 100% gradient over 3 min*; 5 mL/min flow rate
- e) YMC ODSA S3 6.0 x 150 mm; 0 – 100% gradient over 5 min*; 1.5 mL/min flow rate
- f) PHS-PRIMESPHERE C18 4.6 x 30 mm; 0 – 100% gradient over 2 min*; 5 mL/min flow rate
- g) YMC C18 S7 3.0 x 50 mm; 0 – 100% gradient over 4 min*; 5 mL/min flow rate
- h) YMC ODS-A C18 S7 3.0 x 50 mm; 0 - 100% gradient over 2 min*; 5 mL/min flow rate
- i) YMC ODS-A C18 S7 3.0 x 50 mm; 0 - 100% gradient over 1.5 min*; 5 mL/min flow rate
- j) YMC Xterra C18 S7 3.0 x 50 mm; 0 - 100% gradient over 2 min*; 5 mL/min flow rate
- k) YMC Pro-ODS C18 S5 4.6x33 mm; 0 - 100% gradient over 3 min*; 4 mL/min flow rate
- l) YMC ODS-A C18 S7 3.0 x 50 mm; 0 – 100% gradient over 4 min*; 4 mL/min flow rate

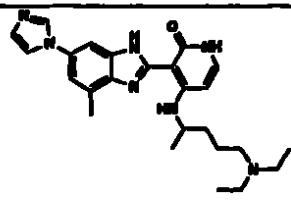
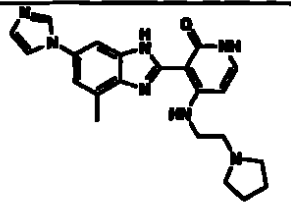
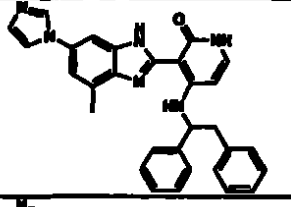
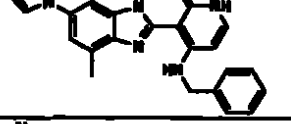
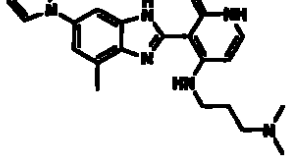
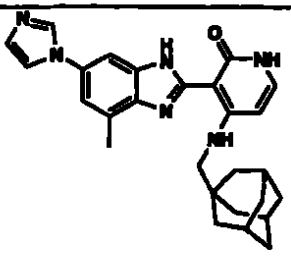
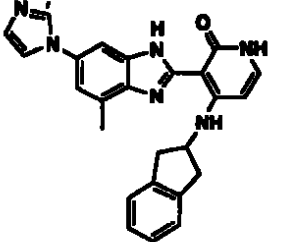
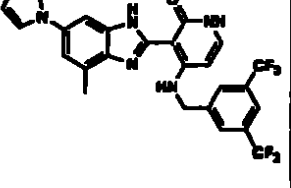
* Gradient begin with 10% methanol/90% water (0.1% TFA) and end with 90% methanol/10% water (0.1% TFA)

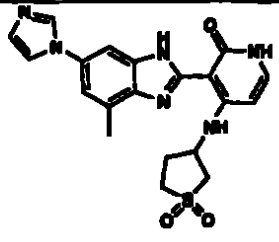
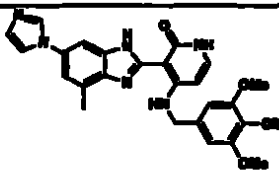
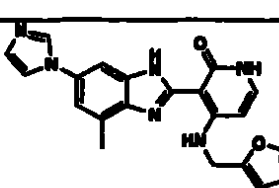
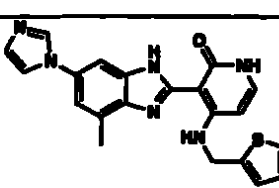
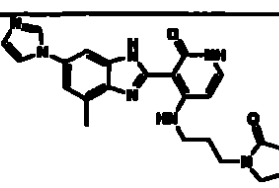
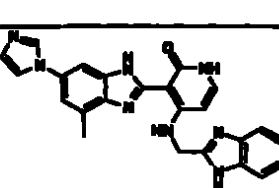
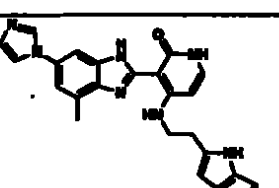
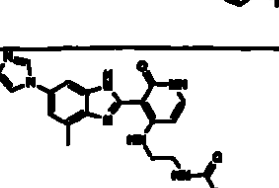
Example #	Name	structure	T (min.)	Mass (M+H) ⁺ m/z
45	4-(2-Fluoro-benzylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.43 (l)	415
46	4-(3,4-Dimethoxy-benzylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.37 (l)	457
47	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		2.17 (a)	398

48	(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (b)	441
49	(R)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (b)	441
50	N-{2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-acetamide		1.55 (l)	392
51	4-(3,4-Dihydroxy-benzylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.97 (l)	429
52	4-[2-(3H-Imidazol-4-yl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.91 (a)	401
53	4-(3,4-Dihydro-2H-quinolin-1-yl)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.88 (a)	423
54	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(pyridin-3-ylmethyl)-amino]-1H-pyridin-2-one		1.83 (a)	398

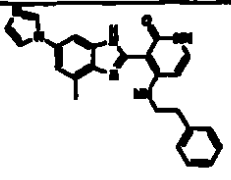
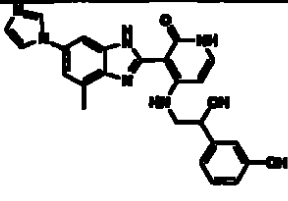
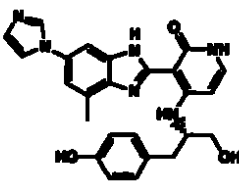
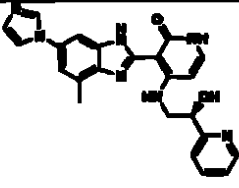
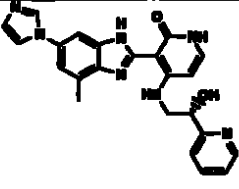
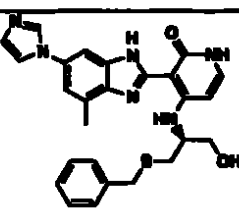
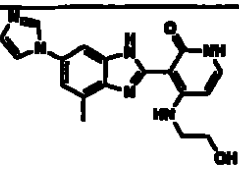
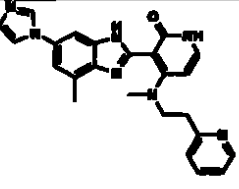
55	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(pyridin-4-ylmethyl)-amino]-1H-pyridin-2-one		1.74 (a)	398
56	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-pyridin-2-yl-ethylamino)-1H-pyridin-2-one		1.99 (a)	412
57	4-[Benzyl-(2-hydroxy-ethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.86 (a)	441
58	(±)-4-[1-(4-Chlorophenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		3.3 (a)	461
59	(±)-4-[(1-Ethylpyrrolidin-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.88 (a)	418
60	(1R,2S)-4-(2-Hydroxy-1-methyl-2-phenylethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		3.01 (a)	441
61	(±)-4-(2-Hydroxy-2-phenylethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		2.96 (a)	427
62	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(3-imidazol-1-yl-		1.94 (a)	415

	propylamino)-1H-pyridin-2-one			
63	(S)-4-(2-Hydroxy-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.27 (b)	427
64	(R)-4-(2-Hydroxy-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.27 (b)	427
65	(±)-4-(1-Benzyl-pyrrolidin-3-ylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.19 (b)	466
66	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(5-nitro-pyridin-2-ylamino)-ethylamino]-1H-pyridin-2-one		1.37 (b)	472
67	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-morpholin-4-yl-ethylamino)-1H-pyridin-2-one		0.98 (b)	420
68	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(2-methyl-5-nitro-1H-imidazol-1-yl)-ethylamino]-1H-pyridin-2-one		1.31 (b)	460
69	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(3-methyl-3H-imidazol-4-yl)-ethylamino]-1H-pyridin-2-one		0.97 (b)	415

70	(±)-4-(4-Diethylamino-1-methyl-butylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.13 (b)	448
71	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-pyrrolidin-1-yl-ethylamino)-1H-pyridin-2-one		0.87 (b)	404
72	(±)-4-(1,2-Diphenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.72 (b)	487
73	4-Benzylamino-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.49 (b)	397
74	4-(3-Dimethylamino-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.03 (b)	392
75	4[(Adamantan-1-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.87 (b)	455
76	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(indan-2-ylamino)-1H-pyridin-2-one		1.57 (b)	423
77	4-(3,5-Bis-trifluoromethyl-benzylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.68 (b)	533

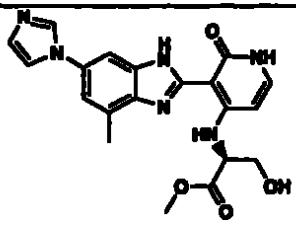
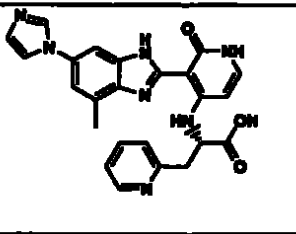
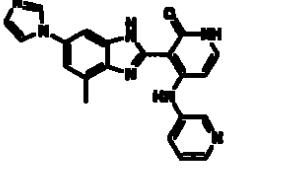
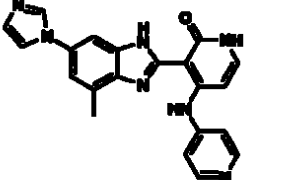
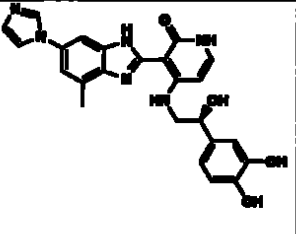
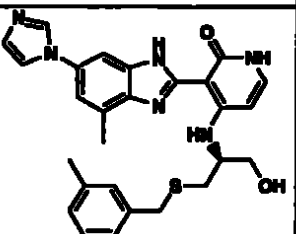
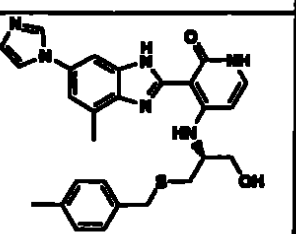
78	(±)-4-(1,1-Dioxo-tetrahydro-1λ ⁶ -thiophene-3-ylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.03 (b)	425
79	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(3,4,5-trimethoxy-benzylamino)-1H-pyridin-2-one		1.33 (b)	487
80	4-[(Furan-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.34 (b)	387
81	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(thiophen-2-ylmethyl)-amino]-1H-pyridin-2-one		1.42 (b)	403
82	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[3-(2-oxo-pyrrolidin-1-yl)-propylamino]-1H-pyridin-2-one		1.15 (b)	432
83	4-[(1H-Benzimidazol-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.98 (b)	437
84	4-[2-(6-Fluoro-1H-indol-2-yl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.53 (b)	468
85	{2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-carbamic acid benzyl		1.31 (b)	484

	ester			
86	(1 <i>S</i> ,2 <i>R</i>)-4-(2-Hydroxy-1,2-diphenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-1 <i>H</i> -pyridin-2-one		1.42 (b)	503
87	(±)-4-(2-[1,3]Dioxolan-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-1 <i>H</i> -pyridin-2-one		1.24 (b)	407
88	(±)-2-[3-(6-Imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-3-phenyl-propionic acid methyl ester		1.44 (b)	469
89	3-(6-Imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-4-(2-2 <i>H</i> -[1,2,3]triazol-2-yl-ethylamino)-1 <i>H</i> -pyridin-2-one		1.05 (b)	402
90	(±)-3-(6-Imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-4-[(1-phenyl-1-pyridin-2-yl-methyl)-amino]-1 <i>H</i> -pyridin-2-one		1.35 (b)	474
91	(1 <i>R</i> ,2 <i>S</i>)-4-(1-Hydroxy-indan-2-ylamino)-3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-1 <i>H</i> -pyridin-2-one		1.35 (b)	439

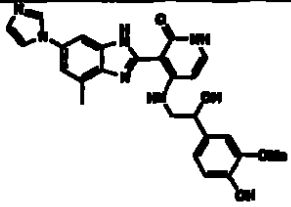
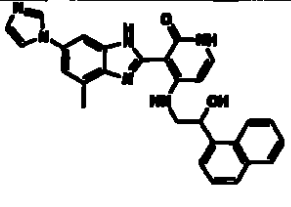
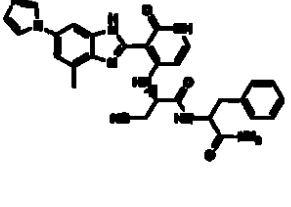
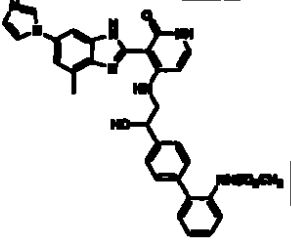
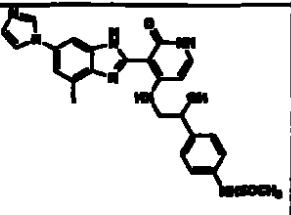
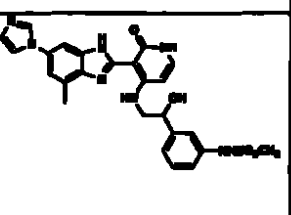
92	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-phenethylamino-1H-pyridin-2-one		1.51 (b)	411
93	(±)-4-[2-Hydroxy-2-(3-hydroxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.15 (a)	443
94	(S)-4-[1-Hydroxymethyl-2-(4-hydroxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.1 (b)	457
95	(R)-4-(2-Hydroxy-2-pyridin-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.09 (a)	428
96	(S)-4-(2-Hydroxy-2-pyridin-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.09 (a)	428
97	(S)-4-(2-Benzylsulfanyl-1-hydroxymethyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.4 (b)	487
98	4-(2-Hydroxy-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.93 (b)	351
99	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-[methyl-(2-pyridin-2-yl-ethylamino)]-1H-pyridin-2-one		0.43 (b)	426

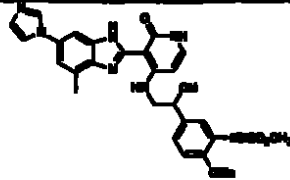
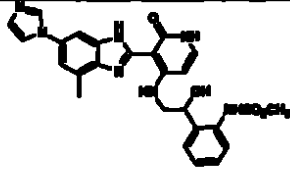
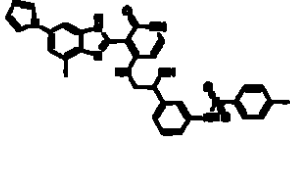
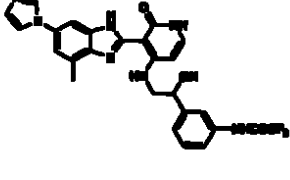
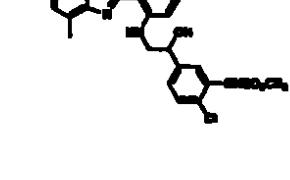
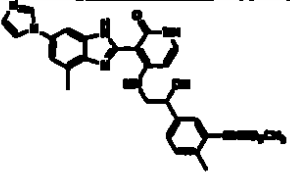
53

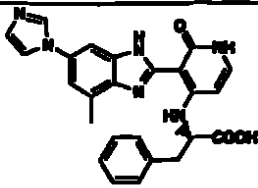
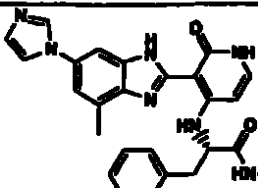
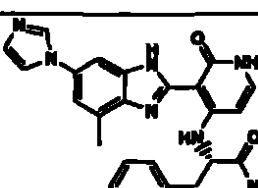
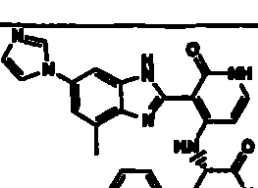
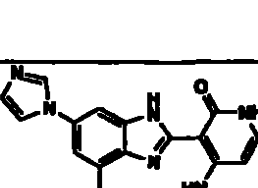
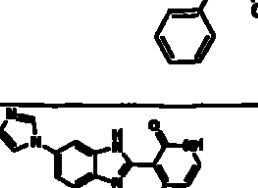
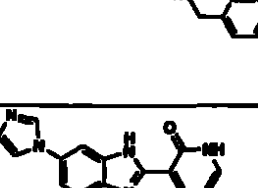
100	(S)-4-(1-Hydroxymethyl-2-pyridin-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.93 (f)	442
101	(R)-4-(1-Hydroxymethyl-2-pyridin-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.94 (f)	442
102	Dimethylamino-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.70 (f)	335
103	(1S,2S)-4-(2-Hydroxy-1-hydroxymethyl-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.10 (b)	457
104	(±)-4-[2-Hydroxy-3-(naphthalen-1-yloxy)-propylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.53 (b)	507
105	(1R,2R)-4-(2-Benzoyloxy-1-hydroxymethyl-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		3.14 (a)	485
106	(S)-3-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-propionic acid benzyl ester		2.95 (a)	485

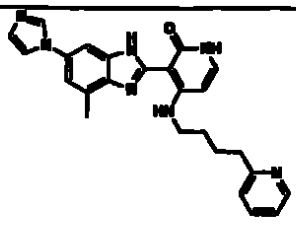
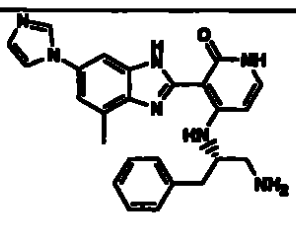
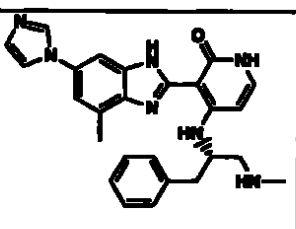
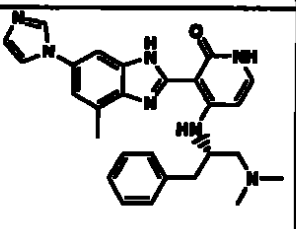
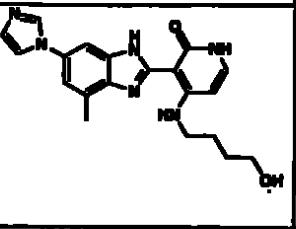
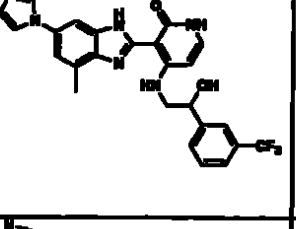
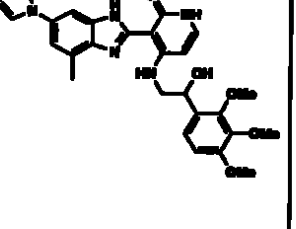
107	(S)-3-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-propionic acid methyl ester		2.29 (a)	409
108	(S)-2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-3-pyridin-2-yl-propionic acid		0.94 (f)	456
109	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(pyridin-3-ylamino)-1H-pyridin-2-one		1.15 (a)	384
110	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(pyridin-4-ylamino)-1H-pyridin-2-one		0.65 (f)	384
111	(S)-4-[2-(3,4-Dihydroxyphenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.04 (b)	459
112	(S)-4-[1-Hydroxymethyl-2-(3-methyl-benzylsulfanyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.49 (b)	501
113	(S)-4-[1-Hydroxymethyl-2-(4-methyl-benzylsulfanyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.49 (b)	501

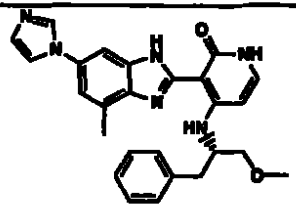
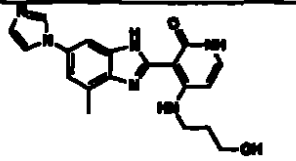
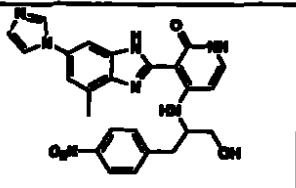
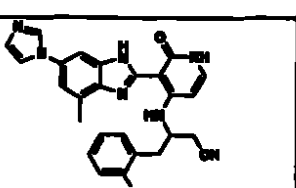
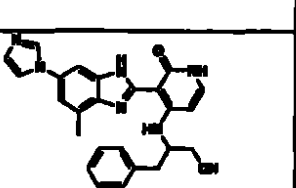
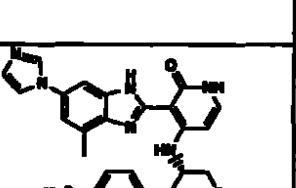
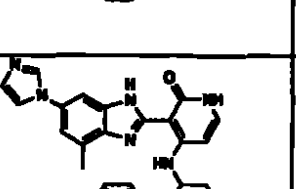
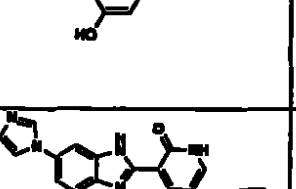
54

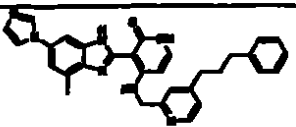
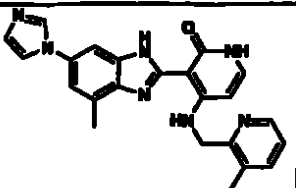
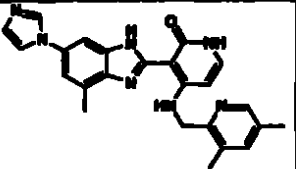
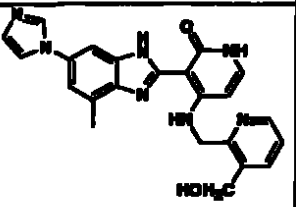
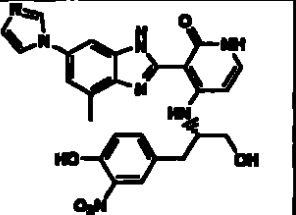
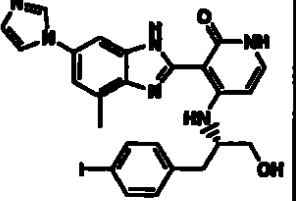
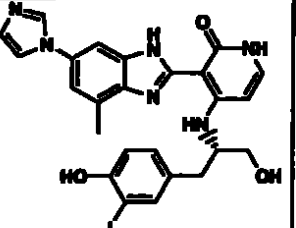
114	(±)-4-[2-Hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.10 (b)	473
115	4-(2-Hydroxy-2-naphthalen-1-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.49 (b)	477
116	(S)-N-(1-Carbamoyl-2-phenyl-ethyl)-3-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-propionamide		1.07 (b)	541
117	(±)-N-(4'-{1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-biphenyl-2-yl)-methanesulfonamide		1.34 (b)	596
118	(±)-N-(4'-{1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-methanesulfonamide		1.11 (b)	520
119	(±)-N-(3-{1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-methanesulfonamide		1.14 (b)	520

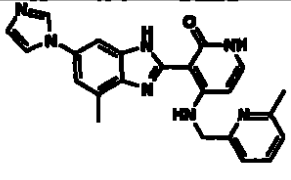
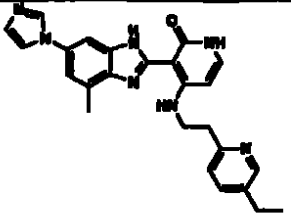
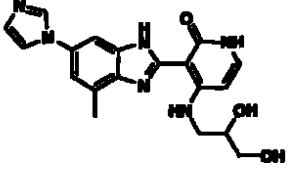
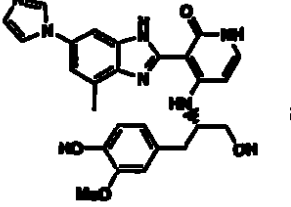
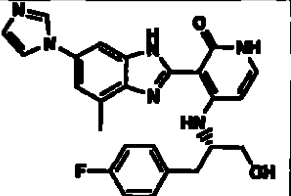
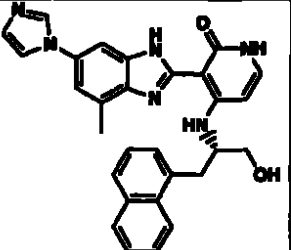
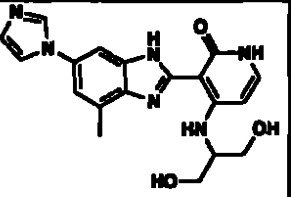
120	(±)-N-(5-(1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-2-methoxy-phenyl)-methanesulfonamide		1.12 (b)	550
121	(±)-N-(2-(1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-phenyl)-methanesulfonamide		1.19 (b)	520
122	(±)-N-(3-(1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-phenyl)-4-methyl-benzenesulfonamide		1.33 (b)	596
123	(±)-2,2,2-Trifluoro-N-(3-(1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-phenyl)-acetamide		2.97 (a)	538
124	(±)-N-(2-Chloro-5-(1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-phenyl)-methanesulfonamide		2.75 (a)	554
125	(±)-N-(5-(1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-2-methyl-phenyl)-methanesulfonamide		2.73 (a)	534

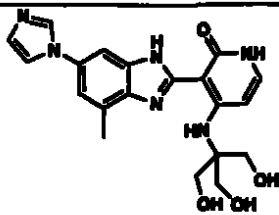
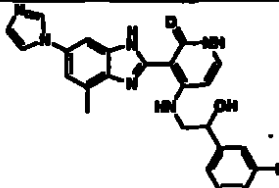
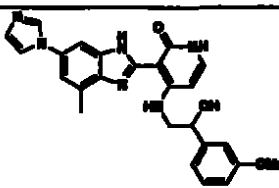
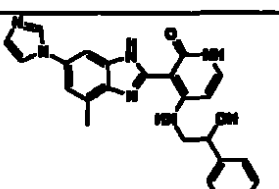
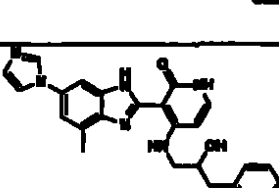
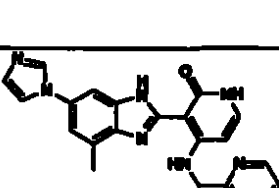
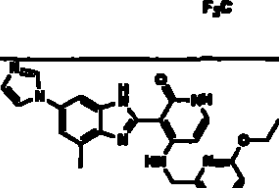
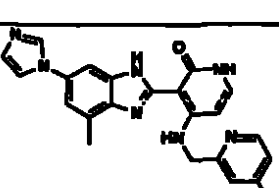
126	(S)-2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-3-phenyl-propionic acid		1.50 (f)	455
127	(S)-2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-N-methyl-3-phenyl-propionamide		1.43 (f)	468
128	(S)-2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-3-phenyl-propionamide		1.39 (f)	454
129	(S)-2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-N,N-dimethyl-3-phenyl-propionamide		1.48 (f)	482
130	(R)-4-(2-Hydroxy-1-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.44 (f)	427
131	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(3-pyridin-2-yl-propylamino)-1H-pyridin-2-one		1.0 (b)	426
132	(S)-4-(1-Benzyl-4-hydroxy-2-oxo-butylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.41 (f)	483

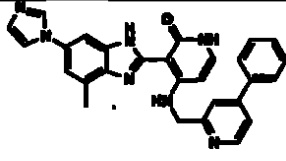
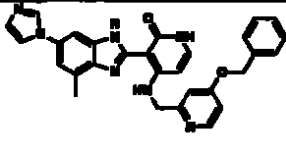
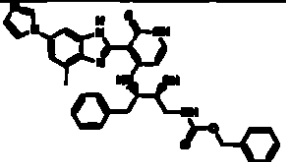
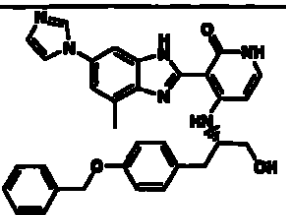
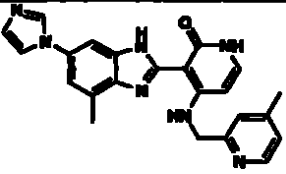
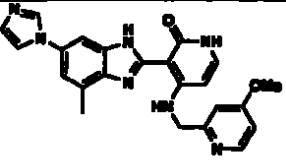
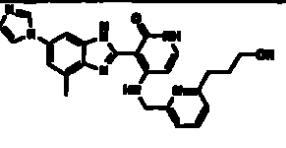
133	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(4-pyridin-2-yl-n-butylamino)-1H-pyridin-2-one		1.06 (d)	440
134	(S)-4-(1-Aminomethyl-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.27 (f)	440
135	(S)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(1-methylaminomethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.27 (f)	454
136	(S)-4-(1-Dimethylaminomethyl-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.25 (f)	468
137	4-(4-Hydroxy-butylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.19 (f)	379
138	(±)-4-[2-Hydroxy-2-(3-trifluoromethyl-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.40 (b)	495
139	(±)-4-[2-Hydroxy-2-(3,4,5-trimethoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.18 (b)	517

140	(S)-4-(1-Benzyl-2-methoxy-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.67 (f)	455
141	4-(3-Hydroxy-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.95 (f)	365
142	(±)-4-[2-Hydroxy-1-(4-nitro-benzyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.51 (a)	486
143	(±)-4-[1-(2-Fluoro-benzyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.57 (a)	459
144	(±)-4-[1-(3-Fluoro-benzyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.57 (a)	459
145	(S)-4-[2-Hydroxy-1-(4-methoxy-benzyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.54 (a)	471
146	(±)-4-[2-Hydroxy-1-(3-hydroxy-benzyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.38 (a)	457
147	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(isoquinolin-3-ylmethyl)-amino]-1H-pyridin-2-one		1.15 (d)	448

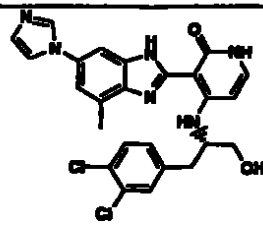
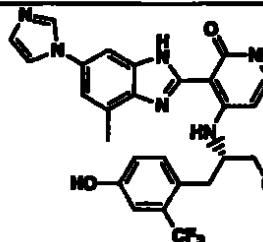
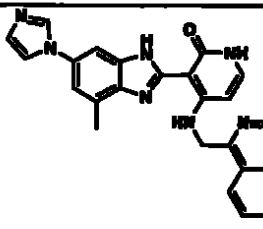
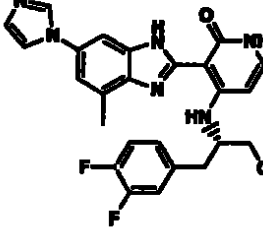
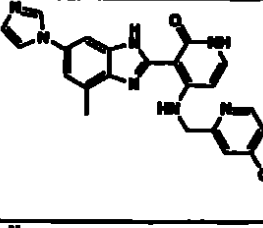
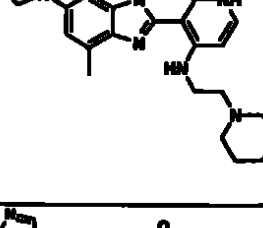
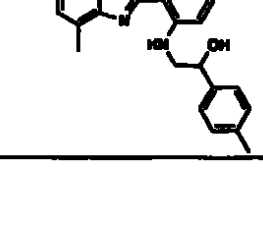
148	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[[4-(3-phenyl-propyl)-pyridin-2-ylmethyl]-amino]-1H-pyridin-2-one		1.31 (d)	516
149	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(3-methyl-pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.00 (d)	412
150	4-[(3,5-Dimethyl-pyridin-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.00 (d)	426
151	4-[(3-Hydroxymethyl-pyridin-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.93 (d)	428
152	(S)-4-[2-Hydroxy-1-(4-hydroxy-3-nitro-benzyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.47 (a)	486
153	(S)-4-[2-Hydroxy-1-(4-iodo-benzyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.73 (a)	567
154	(S)-4-[2-Hydroxy-1-(4-hydroxy-3-iodo-benzyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.44 (a)	583

155	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(6-methyl-pyridin-2-yl)methyl]-amino]-1H-pyridin-2-one		0.71 (b)	412
156	4-[2-(5-Ethyl-pyridin-2-yl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.01 (b)	440
157	(±)-4-(2,3-Dihydroxy-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.11 (a)	381
158	(S)-4-[2-Hydroxy-1-(4-hydroxy-3-methoxy-benzyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.29 (f)	491
159	(S)-4-[1-(4-Fluoro-benzyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.57 (a)	459
160	(S)-4-[2-Hydroxy-1-(naphthalen-1-yl-methyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.71 (a)	491
161	4-(2-Hydroxy-1-hydroxymethyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.00 (f)	381

162	4-[2-Hydroxy-1,1-bis-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.89 (f)	411
163	(±)-4-[2-(3-Fluorophenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.38 (b)	445
164	(±)-4-[2-Hydroxy-2-(3-methoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.35 (b)	457
165	(±)-4-[2-Hydroxy-2-(4-methoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.35 (b)	457
166	(±)-4-(2-Hydroxy-3-phenyl-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.44 (b)	441
167	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.53 (d)	466
168	4-[(6-Ethoxy-pyridin-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.51 (d)	442
169	4-[(4-Chloro-pyridin-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.38 (d)	432

170	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(4-phenyl-pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.24 (d)	474
171	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(4-benzyloxy-pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.14 (d)	504
172	(2S,3S)-{2-Hydroxy-3-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-4-phenyl-butyl}-carbamic acid benzyl ester		1.59 (f)	604
173	(S)-4-[1-(4-Benzyloxy-benzyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.74 (f)	547
174	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(4-methyl-pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		0.95 (d)	412
175	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(4-methoxy-pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		0.92 (d)	428
176	4-[[6-(3-Hydroxy-propyl)-pyridin-2-ylmethyl]-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.96 (d)	456

177	4-[(6-Aminomethyl-pyridin-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.99 (b)	427
178	N-(6-{[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-methyl}-pyridin-2-ylmethyl)-formamide		1.02 (b)	455
179	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(quinolin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.16 (b)	448
180	4-(2-Cyclohex-1-enyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.61 (b)	415
181	(S)-4-[2-(4-tert-Butoxy-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.61 (f)	513
182	(±)-4-[2-(2,3-Dichlorophenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.52 (b)	495
183	(±)-4-[2-(3,4-Difluorophenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.34 (b)	463

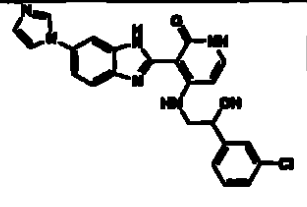
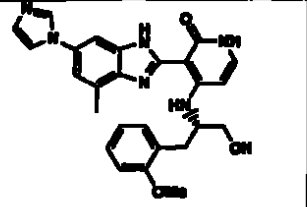
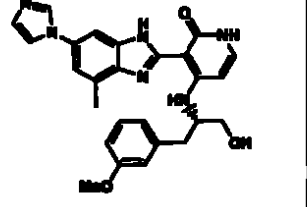
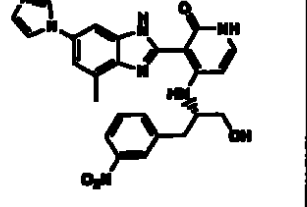
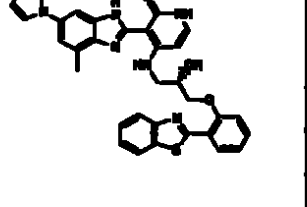
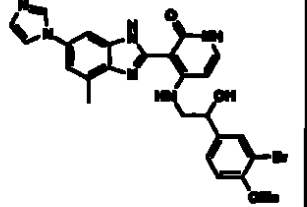
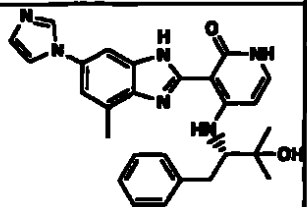
184	(S)-4-[2-(3,4-Dichlorophenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.67 (f)	509
185	(S)-4-[1-Hydroxymethyl-2-(4-hydroxy-2-trifluoromethyl-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.46 (f)	525
186	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(isoquinolin-1-ylmethyl)-amino]-1H-pyridin-2-one		1.14 (d)	448
187	(S)-4-[2-(3,4-Difluorophenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.52 (f)	477
188	4-[(4-Hydroxy-pyridin-2-ylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.91 (d)	414
189	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-piperidin-1-yl-ethylamino)-1H-pyridin-2-one		0.92 (b)	418
190	(±)-4-(2-Hydroxy-2-p-tolyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		5.74 (c)	441

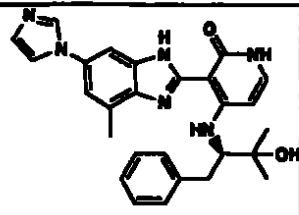
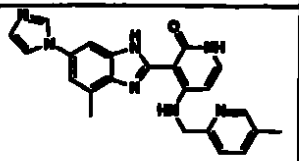
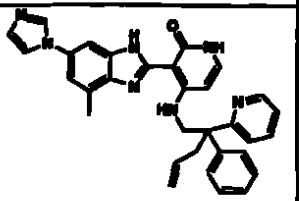
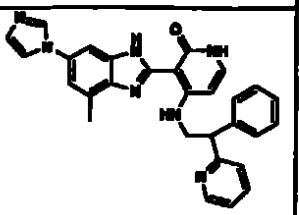
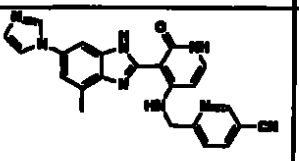
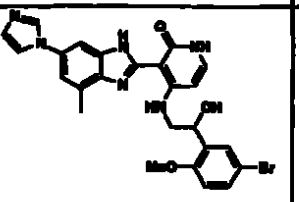
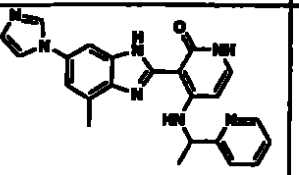
191	4-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		6.40 (c)	563
192	(±)-4-[2-(3-Chlorophenyl)-2-methoxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		6.5 (c)	475
193	4-[(4-Hydroxymethylpyridin-2-yl)methyl-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.9 (b)	428
194	(±)-4-[2-(3,5-Dichlorophenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.54 (b)	495
195	(±)-4-[(4-tert-Butyl-1-hydroxy-cyclohexylmethyl)-amino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		3.82 (a)	475
196	(±)-{2-Hydroxy-3-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-propyl}-carbamic acid tert-butyl ester		1.23 (b)	480
197	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(3,3,3-trifluoro-2-hydroxy-propylamino)-1H-pyridin-2-one		1.17 (b)	419

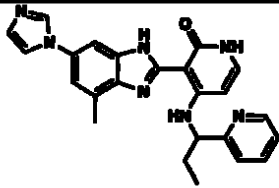
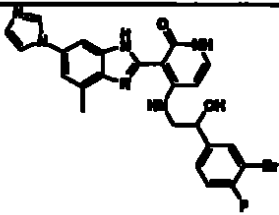
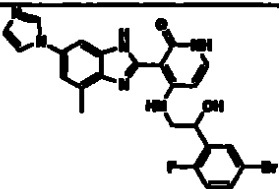
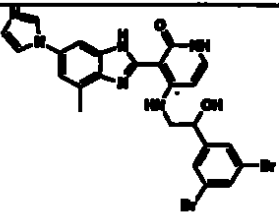
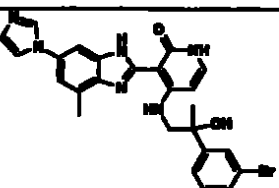
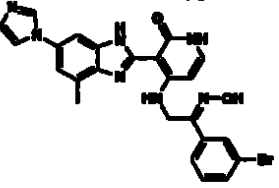
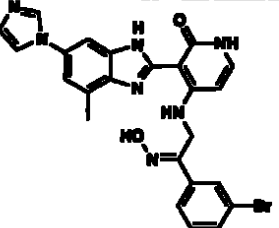
198	(±)-4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.40 (b)	479
199	(±)-4-(2-Hydroxy-2- <i>m</i> -tolyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.37 (b)	441
200	(<i>S</i>)-4-(1-Hydroxymethyl-3-phenyl-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.56 (f)	455
201	(<i>S</i>)-4-(1-Hydroxymethyl-2- <i>p</i> -tolyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.57 (f)	455
202	(<i>S</i>)-4-[2-(3-Fluorophenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (f)	459
203	(1 <i>S</i> ,2 <i>R</i>)-4-(1-Benzyl-2,4-dihydroxy-butylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.39 (f)	485
204	(<i>S</i>)-4-[1-Hydroxymethyl-2-(3-trifluoromethyl-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.56 (f)	509

205	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(pyrimidin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.16 (b)	399
206	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(pyrazin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.14 (b)	399
207	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-phenyl-1-pyridin-2-yl-ethylamino)-1H-pyridin-2-one		1.26 (b)	488
208	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(3-phenyl-1-pyridin-2-yl-propylamino)-1H-pyridin-2-one		1.34 (d)	502
209	(±)-4-[2-(3-Fluoro-phenyl)-1-pyridin-2-yl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.31 (d)	506
210	(±)-4-[2-(3-Chloro-phenyl)-1-pyridin-2-yl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.39 (d)	522
211	4-[2-(2-Fluoro-phenyl)-1-pyridin-2-yl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.33 (d)	506

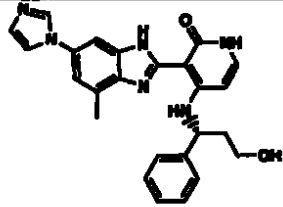
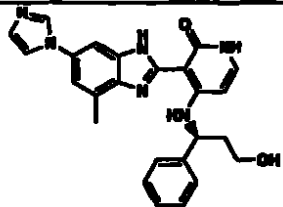
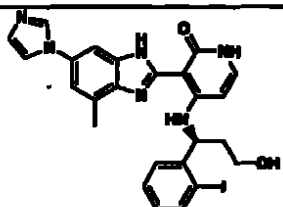
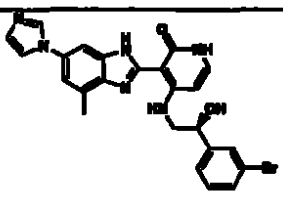
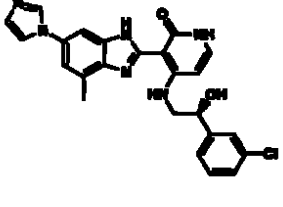
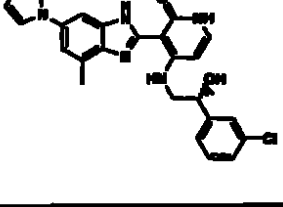
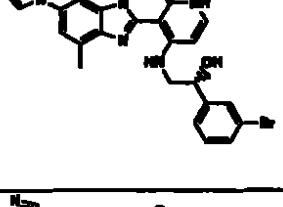
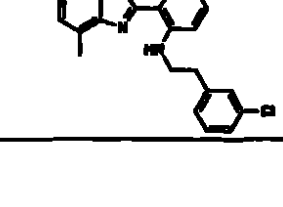
212	(±)-4-[2-(3-Bromo-phenyl)-1-pyridin-2-yl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.40 (d)	566
213	(±)-4-[2-(2-Bromo-phenyl)-1-pyridin-2-yl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.45 (d)	566
214	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(2-iodo-phenyl)-1-pyridin-2-yl-ethylamino]-1H-pyridin-2-one		1.47 (d)	614
215	(±)-4-[2-(2-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.21 (i)	461
216	4-[3-(4-Cyclopentylamino-6-propoxy-[1,3,5]triazin-2-yloxy)-propylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.67 (b)	585
217	(±)-3-[1-Hydroxy-2-[3-(6-imidazol-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl]-benzonitrile		1.20 (b)	452
218	(±)-4-(2-Biphenyl-3-yl-2-hydroxy-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.51 (b)	503

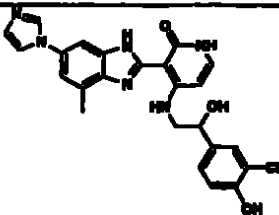
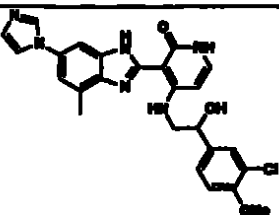
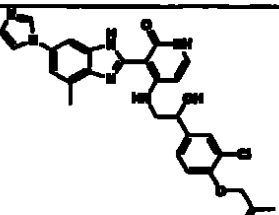
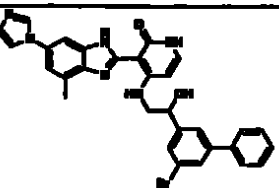
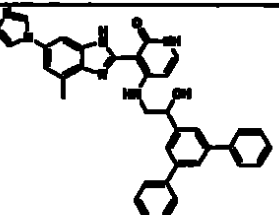
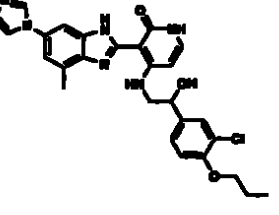
219	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.35 (f)	447
220	(S)-4-[1-Hydroxymethyl-2-(2-methoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.52 (f)	471
221	(S)-4-[1-Hydroxymethyl-2-(3-methoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.42 (f)	471
222	(S)-4-[1-Hydroxymethyl-2-(3-nitro-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.27 (f)	486
223	(S)-4-[3-(2-Benzothiazol-2-yl-phenoxy)-2-hydroxy-propylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.47 (j)	590
224	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.35 (j)	535
225	(S)-4-(1-Benzyl-2-hydroxy-2-methyl-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		22.07	HPLC

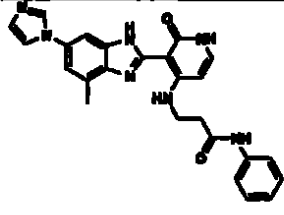
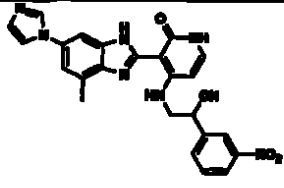
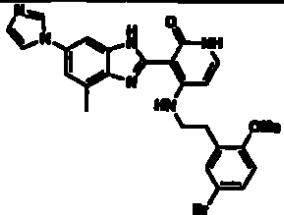
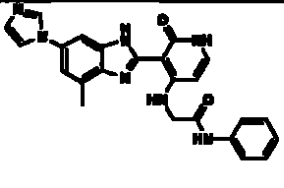
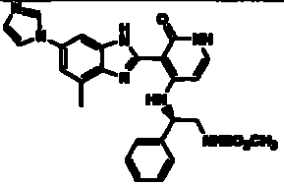
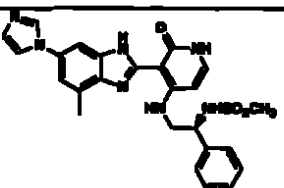
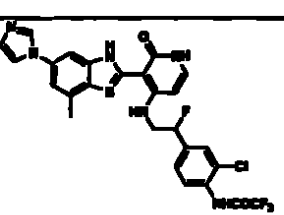
226	(R)-4-(1-Benzyl-2-hydroxy-2-methyl-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		22.09	HPLC
227	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(5-methyl-pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		0.99 (d)	412
228	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-phenyl-2-pyridin-2-yl-pent-4-enylamino)-1H-pyridin-2-one		1.41 (d)	528
229	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(2-phenyl-2-pyridin-2-yl-ethylamino)-1H-pyridin-2-one		1.22 (d)	488
230	6-[[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-methyl]-nicotinonitrile		1.22 (d)	423
231	(±)-4-[2-(5-Bromo-2-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.27 (i)	535
232	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(1-pyridin-2-yl-ethylamino)-1H-pyridin-2-one		1.12 (d)	412

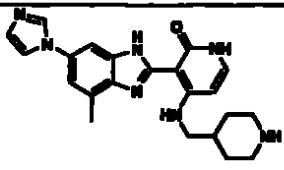
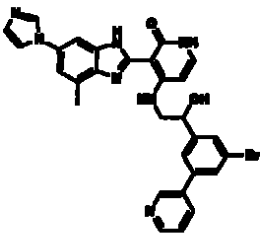
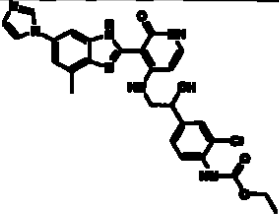
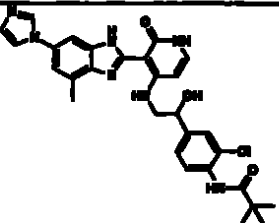
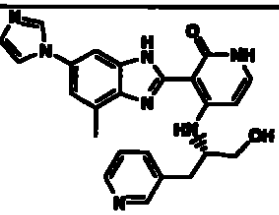
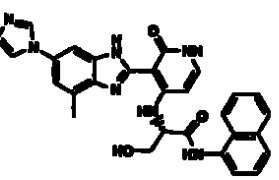
233	(±)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(1-pyridin-2-yl-propylamino)-1H-pyridin-2-one		1.17 (d)	426
234	(±)-4-[2-(3-Bromo-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.24 (i)	523
235	(±)-4-[2-(5-Bromo-2-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.15 (i)	523
236	(±)-4-[2-(3,5-Dibromophenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.30 (i)	583
237	(±)-4-[2-(3-Bromophenyl)-2-hydroxypropylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.90 (d)	519
238	(E)-4-[2-(3-Bromophenyl)-2-hydroxyiminoethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		7.81 (e)	518
239	(Z)-4-[2-(3-Bromophenyl)-2-hydroxyiminoethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		7.91 (e)	518

63

240	(R)-4-(3-Hydroxy-1-phenyl-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (f)	441
241	(S)-4-(3-Hydroxy-1-phenyl-propylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (f)	441
242	(S)-4-[3-Hydroxy-1-(2-iodo-phenyl)-propylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.61 (f)	567
243	(S)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.35 (b)	505
244	(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.30 (b)	461
245	(R)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.37 (b)	461
246	(R)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.35 (b)	505
247	4-[2-(3-Chloro-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.53 (b)	445

248	(±)-4-[2-(3-Chloro-4-hydroxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.15 (b)	477
249	(±)-4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.24 (b)	491
250	(±)-4-[2-[3-Chloro-4-(2-methyl-allyloxy)-phenyl]-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.46 (b)	531
251	(±)-[2-(5-Bromo-biphenyl-3-yl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.44 (i)	581
252	(±)-4-(2-Hydroxy-2-[1,1',3',1'']terphenyl-5'-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (i)	579
253	(±)-4-[2-(3-Chloro-4-propoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.76 (b)	519

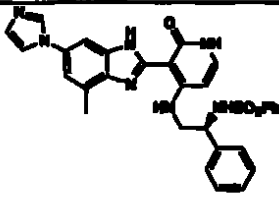
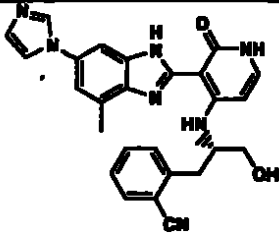
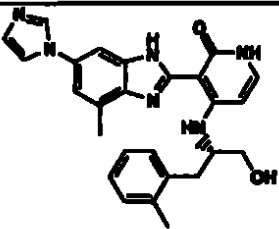
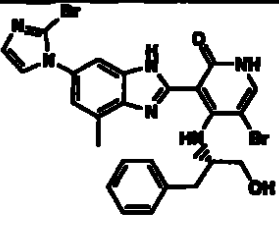
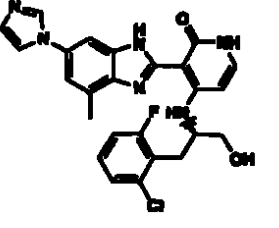
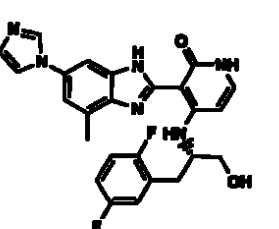
254	3-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-N-phenyl-propionamide		1.13 (i)	454
255	(±)-4-[2-Hydroxy-2-(3-nitro-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.20 (i)	472
256	4-[2-(5-Bromo-2-methoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.51 (i)	519
257	2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-N-phenyl-acetamide		1.25 (i)	440
258	(R)-N-{2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-2-phenylethyl}-methanesulfonamide		1.35 (h)	504
259	(S)-N-{2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-1-phenylethyl}-methanesulfonamide		1.32 (h)	504
260	(±)-N-(2-Chloro-4-{1-fluoro-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-2,2,2-trifluoroacetamide		1.30 (b)	574

261	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)-amino]-1H-pyridin-2-one		0.90 (b)	404
262	(±)-4-[2-(3-Bromo-5-pyridin-3-yl-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.18 (a)	582
263	(±)-(2-Chloro-4-{1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-carbamic acid ethyl ester		1.36 (b)	548
264	(±)-N-(2-Chloro-4-{1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-2,2-dimethyl-propionamide		1.42 (b)	560
265	(S)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(1-hydroxymethyl-2-pyridin-3-yl-ethylamino)-1H-pyridin-2-one		0.78 (b)	442
266	(S)-3-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-N-naphthalen-1-yl-propionamide		1.41 (b)	520

267	(S)-3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[1-(1H-indol-3-ylmethyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.22 (b)	480
268	(S)-4-[3-Hydroxy-1-(1H-imidazol-4-yl)-propylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		0.75 (b)	431
269	(±)-4-[2-(3,4-Dichlorophenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (b)	495
270	(±)-1-(2-Chloro-ethyl)-3-(2-chloro-4-[1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl]-phenyl)-urea		1.26 (b)	581
271	(±)-(2-Chloro-4-[1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl]-phenyl)-carbamic acid isopropyl ester		1.41 (b)	562
272	(±)-(2-Chloro-4-[1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl]-phenyl)-carbamic acid isobutyl ester		1.49 (b)	576
273	(S)-3-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-		1.36 (b)	520

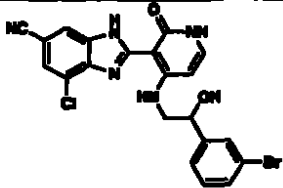
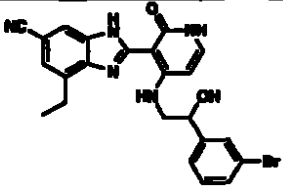
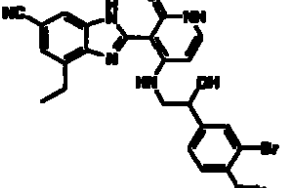
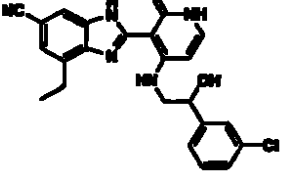
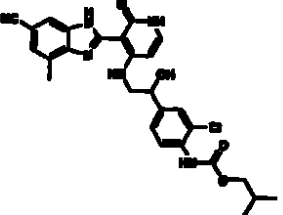
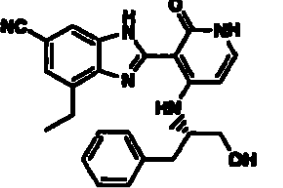
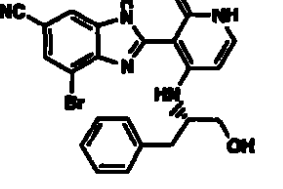
	pyridin-4-ylamino]- <i>N</i> -naphthalen-2-yl-propionamide			
274	(<i>S</i>)-3-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]- <i>N</i> -(4-methoxy-naphthalen-2-yl)-propionamide		1.45 (b)	550
275	(<i>S</i>)-Ethanesulfonic acid (2-[3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-1-phenyl-ethyl)-amide		1.47 (b)	518
276	(±)-(2-Chloro-4-(1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-phenyl)-carbamic acid methyl ester		1.23 (b)	534
277	(±)-4-[1-Hydroxymethyl-2-(2-hydroxy-3-methyl-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-1 <i>H</i> -pyridin-2-one		1.29 (b)	471
278	(<i>S</i>)-4-[2-(5-Bromo-2-methoxy-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-1 <i>H</i> -pyridin-2-one		1.48 (b)	549
279	4-(2 <i>S</i> -Hydroxy-1-indan-1-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1 <i>H</i> -benzimidazol-2-yl)-1 <i>H</i> -pyridin-2-one		1.42 (b)	467

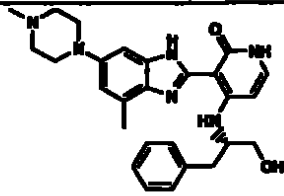
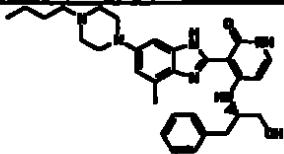
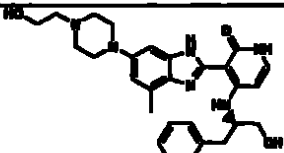
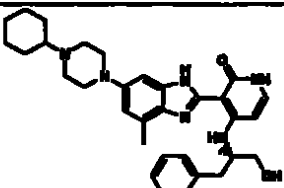
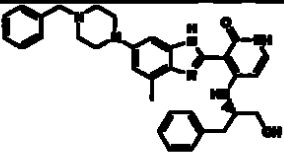
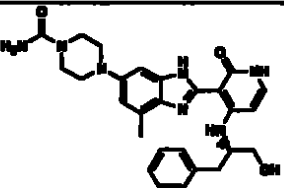
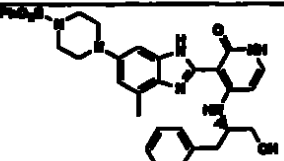
280	(±)-4-[2-(3-Bromo-4-methyl-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.43 (b)	519
281	3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(1H-indol-5-yl)-ethylamino]-1H-pyridin-2-one		1.54 (b)	450
282	(S)-3-(5-Bromo-2-methoxy-phenyl)-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-propionic acid		1.09 (b)	563
283	(S)-Propane-2-sulfonic acid {2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-1-phenyl-ethyl}-amide		1.34 (b)	532
284	(S)-Thiophen-2-sulfonic acid {2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-1-phenyl-ethyl}-amide		2.45 (a)	572
285	(S)-N-{2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-1-phenyl-ethyl}-4-methanesulfonyl-benzenesulfonamide		1.34 (b)	644

286	(S)-N-{2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-1-phenylethyl}-benzenesulfonamide		1.60 (b)	566
287	(S)-2-{3-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-propyl}-benzonitrile		1.16 (b)	466
288	(S)-4-(1-Hydroxymethyl-2-o-tolyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.33 (b)	455
289	(S)-5-Bromo-3-[6-(2-bromo-imidazol-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.36 (b)	597
290	(S)-4-[2-(2-Chloro-6-fluoro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.40 (a)	493
291	(S)-4-[2-(2,5-Difluoro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.44 (a)	477

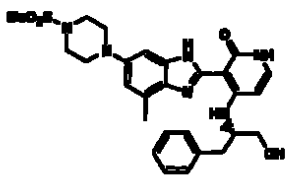
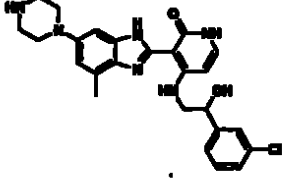
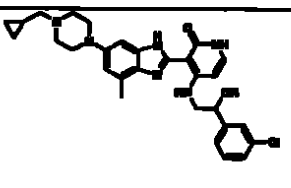
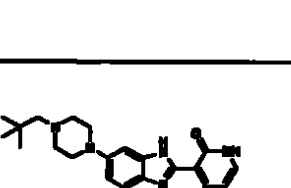
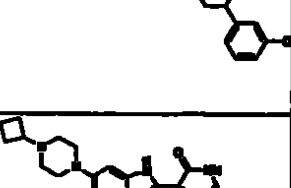
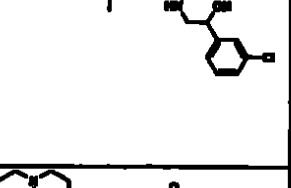
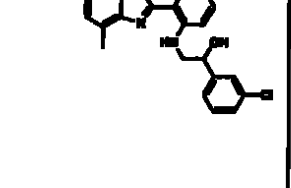
292	(S)-4-[1-hydroxymethyl-2-(2-methoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.52 (f)	471
293	(S)-4-[2-(2,6-Difluoro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.42 (a)	477
294	(S)-4-[2-(2,6-Dichloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.42 (a)	509
295	(S)-4-[1-Hydroxymethyl-2-(2-trifluoromethoxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.48 (a)	525
296	(S)-N-{2-[3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-3-phenyl-propyl}-methanesulfonamide		1.31 (a)	518
297	(S)-2-{4-[2-(2-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile		1.80 (b)	434
298	(S)-2-[4-(1-Hydroxymethyl-2-pyridin-3-yl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-		1.07 (b)	401

	benzimidazole-5-carbonitrile			
299	(S)-2-[4-(1-Hydroxymethyl-2-pyridin-4-yl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile		1.16 (b)	401
300	(S)-2-[4-(1-Hydroxymethyl-2-thiophen-2-yl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile		1.73 (b)	406
301	(S)-2-[4-(2-Benzo[b]thiophen-3-yl-1-hydroxymethyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile		1.84 (b)	456
302	7-Methyl-2-[(2-oxo-4-[(pyridin-2-ylmethyl)-amino]-1,2-dihydro-pyridin-3-yl)-3H-benzimidazole-5-carbonitrile		1.30 (b)	357
303	(±)-2-[4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-chloro-3H-benzimidazole-5-carbonitrile		1.74 (d)	514
304	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-chloro-3H-benzimidazole-5-carbonitrile		1.78 (d)	440

305	(±)-2-[4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-chloro-3H-benzimidazole-5-carbonitrile		1.77 (d)	484
306	(±)-2-[4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-ethyl-3H-benzimidazole-5-carbonitrile		1.82 (d)	478
307	(±)-2-[4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-ethyl-3H-benzimidazole-5-carbonitrile		1.76 (d)	508
308	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-ethyl-3H-benzimidazole-5-carbonitrile		1.80 (d)	434
309	(±)-(2-Chloro-4-[2-[3-(6-cyano-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-1-hydroxy-ethyl]-phenyl)-carbamic acid isobutyl ester		1.93 (b)	535
310	(S)-7-Ethyl-2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carbonitrile		1.75 (d)	414
311	(S)-7-Bromo-2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carbonitrile		1.91 (b)	464

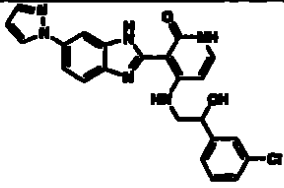
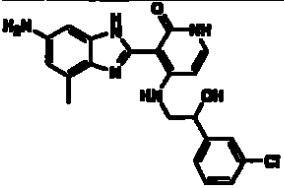
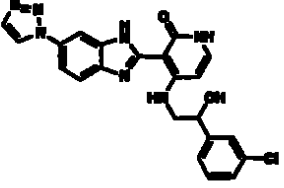
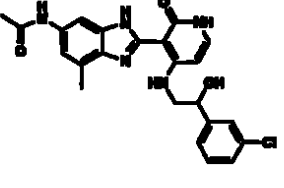
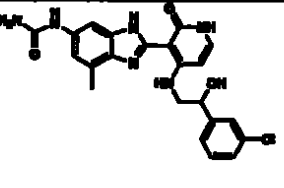
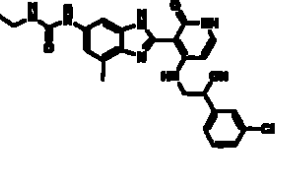
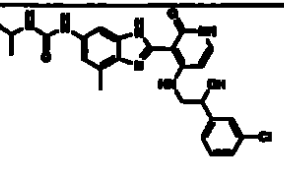
312	(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.08 (f)	473
313	(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(4-n-butyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.29 (k)	515
314	(S)-3-[6-[4-(2-Hydroxyethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.62 (k)	503
315	(S)-3-[6-(4-Cyclohexyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.34 (f)	541
316	(S)-3-[6-(4-benzyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.93 (f)	549
317	(S)-4-{2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl}-piperazine-1-carboxylic acid amide		1.26 (f)	502
318	(S)-3-[6-(4-Benzenesulfonyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		2.30 (k)	599

69

319	(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[6-(4-methanesulfonyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.93 (k)	537
320	(±)-4-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.90 (f)	479
321	(±)-4-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]-3-[6-(4-cyclopropylmethyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.97 (k)	533
322	(±)-4-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]-3-[6-[4-(2,2-dimethyl-propyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		2.06 (k)	549
323	(±)-4-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]-3-[6-(4-cyclobutyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.97 (k)	533
324	(±)-4-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]-3-[6-(4-ethyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.88 (k)	507
325	(±)-4-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]-3-[6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.82 (k)	524

326	(±)-[4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzoimidazol-5-yl)-piperazin-1-yl]-acetic acid ethyl ester		2.03 (k)	565
327	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-dimethylamino-2,2-dimethyl-propyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.84 (k)	592
328	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.19 (a)	480
329	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.21 (a)	524
330	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.16 (a)	554
331	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-[4-(tetrahydropyran-4-yl)-piperazin-1-yl]-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.19 (f)	563
332	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4-imidazol-2-ylmethyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.19 (f)	559

333	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(4-propyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.19 (f)	521
334	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.08 (f)	576
335	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-[6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.79 (f)	567
336	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.83 (f)	523
337	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.72 (f)	553
338	(±)-3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.90 (f)	565
339	(±)-3-(6-Amino-5-methyl-1H-benzimidazol-2-yl)-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.41 (j)	454

340	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-pyrazol-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.86 (f)	447
341	(±)-3-(6-Amino-4-methyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.51 (f)	410
342	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-[1,2,3]triazol-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		2.04 (f)	448
343	(±)-N-(2-{4-[2-(3-Chloro-Phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-acetamide		1.62 (f)	452
344	(±)-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-urea		1.49 (f)	453
345	(±)-1-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-3-ethyl-urea		1.64 (f)	481
346	(±)-1-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-3-isopropyl-urea		1.71 (f)	495

347	(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(2-morpholin-4-yl-ethylamino)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.05 (f)	503
348	(±)-4-[2-(3-Bromophenyl)-2-hydroxyethylamino]-3-(4,5,6-trifluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.76 (d)	479
349	4-[(Pyridin-2-ylmethyl)amino]-3-(4,5,6-trifluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.36 (d)	372
350	(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-(4,5,6-trifluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.73 (d)	415
351	3-(4,6-Dibromo-1H-benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)amino]-1H-pyridin-2-one		1.66 (d)	474
352	(±)-4-[2-(3-Bromophenyl)-2-hydroxyethylamino]-3-(4,6-dibromo-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.95 (d)	581
353	(S)-3-(4,6-Dibromo-1H-benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.92 (d)	517

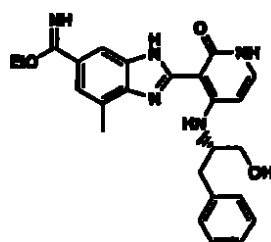
354	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(5,6-dichloro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.85 (d)	493
355	3-(5,6-Dichloro-1H-benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.48 (d)	386
356	(S)-3-(5,6-Dichloro-1H-benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.82 (d)	429
357	(±)-3-(4,6-Bis-trifluoromethyl-1H-benzimidazol-2-yl)-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.56 (b)	561
358	3-(4,6-Bis-trifluoromethyl-1H-benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.39 (b)	454
359	(S)-3-(4,6-Bis-trifluoromethyl-1H-benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.53 (b)	497
360	(±)-3-(4,6-Bis-trifluoromethyl-1H-benzimidazol-2-yl)-4-[2-(3-bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.51 (b)	591
361	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.54 (b)	527

362	3-(4-Chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.34 (b)	420
363	(S)-3-(4-Chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.51 (b)	463
364	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.50 (b)	557
365	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.42 (b)	493
366	4-[(Pyridin-2-ylmethyl)-amino]-3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.16 (b)	386
367	(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.41 (b)	429
368	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.38 (b)	523
369	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(5-fluoro-6-imidazol-1-yl-1H-benzimidazol-2-yl)-1H-		1.10 (b)	509

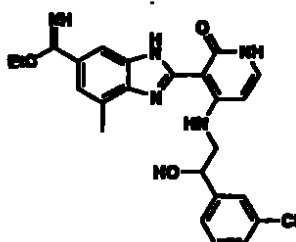
	pyridin-2-one			
370	3-(5-Fluoro-6-imidazol-1-yl-1H-benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		0.73 (b)	402
371	(S)-3-(5-Fluoro-6-imidazol-1-yl-1H-benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.04 (b)	445
372	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(5-fluoro-6-imidazol-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.05 (b)	539
373	(±)-3-(4-Bromo-6-trifluoromethyl-1H-benzimidazol-2-yl)-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.97 (d)	571
374	(±)-3-(4-Bromo-6-trifluoromethyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.95 (d)	527
375	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4,6-difluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.72 (d)	461
376	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4,6-difluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.70 (d)	417

377	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4,6-difluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.65 (d)	491
378	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-methyl-imidazol-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.38 (d)	475
379	(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-imidazol-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.35 (d)	549
380	(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(5,6-difluoro-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.67 (b)	461
381	3-(5,6-Difluoro-1H-benzimidazol-2-yl)-4-[(pyridin-2-yl-methyl)-amino]-1H-pyridin-2-one		1.18 (b)	354
382	6-Hydroxy-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one		0.96 (f)	309
383	(±)-6-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one		2.30 (f)	462

Intermediate Imidate Formation (Scheme IV, 13)



- 5 (S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboximidic ethyl ester: To a suspension of (S)-2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile (0.8 g, 2.0 mmol) in ethanol (anhydrous, 80 mL) was bubbled HCl (anhydrous) at 0°C until saturation. The mixture became a
- 10 clear solution after a few minutes of bubbling and the solution was stirred at room temperature for 14 h. After concentration *in vacuo*, the crude product (0.89 g, 100%) was directly used for the next step without purification. LCMS (M+H)⁺ m/z 446 (t = 1.55 min).

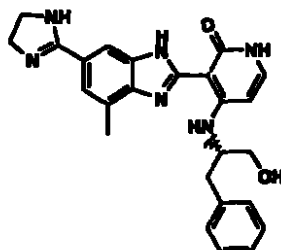


- 15 (±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboximidic ethyl ester: The title compound was prepared using the General Procedure for Imidate Formation. LCMS (M+H)⁺ m/z 466 (t = 1.43 min.).

20

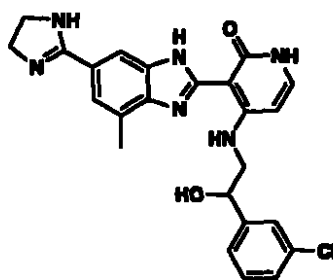
General Procedure for Examples 384 - 397 – Imidazoline Formation (Scheme IV, 14)

Example 384

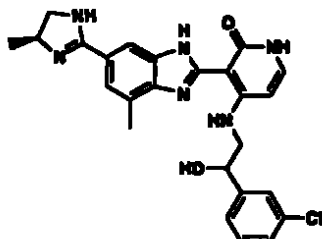


(S)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one: The crude imidate ester (60 mg, 0.135 mmol) was diluted with methanol followed by addition of ethylenediamine (24 mg, 0.40 mmol). The reaction mixture was heated to reflux for 6 h. After concentration *in vacuo*, the residue was purified by prep. HPLC to yield the title compound (37 mg, 62%). ¹H NMR (300 MHz, CD₃OD) δ 7.94 (1H, s), 7.50 (1H, s), 7.12 – 7.30 (6H, m), 6.16 (1H, d, *J* = 7.7 Hz), 4.04 – 4.10 (5H, m), 3.75 – 3.77 (2H, m), 3.15 (1H, dd, *J* = 5.2, 13.6 Hz), 2.96 (1H, dd, *J* = 8.1, 13.6 Hz), 2.67 (3H, s). LCMS (M+H)⁺ *m/z* 443 (*t* = 1.50 min.).

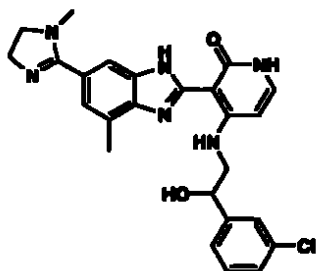
Example 385



(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 7.93 (1H, s), 7.54 (1H, s), 7.23 – 7.45 (5H, m), 6.26 (1H, d, *J* = 7.6 Hz), 5.01 (1H, t, *J* = 6.3 Hz), 4.01 (4H, s), 3.78 (1H, dd, *J* = 4.7, 13.5 Hz), 3.67 (1H, dd, *J* = 6.6, 13.5 Hz), 2.66 (3H, s). LCMS (M+H)⁺ *m/z* 463 (*t* = 1.54 min)

Example 386

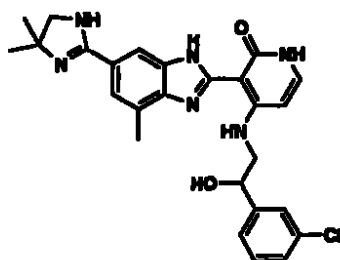
4-[2-(3-Chloro-phenyl)-2*R*-hydroxy-ethylamino]-3-[4-methyl-6-(4*S*-methyl-4,5-
 5 dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyridin-2-one and 4-[2-
 (3-Chloro-phenyl)-2*S*-hydroxy-ethylamino]-3-[4-methyl-6-(4*S*-methyl-4,5-
 dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyridin-2-one: ¹H NMR
 (300 MHz, CD₃OD) δ 7.90 (2H, s), 7.53 (2H, s), 7.22 – 7.47 (10H, m), 6.23 (2H, d, *J*
 = 7.5 Hz), 5.00 (2H, t, *J* = 6.4 Hz), 4.49 – 4.57 (2H, m), 4.21 (2H, t, *J* = 11.0 Hz),
 10 3.61 – 3.78 (6H, m), 2.63 (6H, s), 1.48 (6H, d, *J* = 6.3 Hz). LCMS (M+H)⁺ *m/z* 477 (*t*
 = 1.71 min.).

Example 387

15

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(1-methyl-4,5-
 dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyridin-2-one: ¹H NMR
 (300 MHz, CD₃OD) δ 7.94 (1H, s), 7.57 (1H, s), 7.23 – 7.52 (5H, m), 6.22 (1H, d, *J* =
 7.5 Hz), 4.99 (1H, m), 4.00 – 4.15 (2H, m), 3.57 – 3.75 (4H, m), 2.77 (3H, s), 2.61
 20 (3H, s). LCMS (M+H)⁺ *m/z* 477 (*t* = 1.60 min.).

Example 388

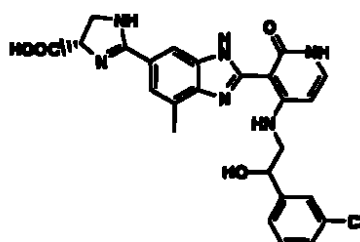


(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4,4-dimethyl-4,5-

dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H

- 5 NMR (300 MHz, CD₃OD) δ 7.89 (1H, s), 7.52 (1H, s), 7.22 – 7.45 (5H, m), 6.19 (1H, d, *J* = 7.4 Hz), 4.99 (1H, t, *J* = 6.2 Hz), 3.84 (2H, s), 3.78 (1H, dd, *J* = 4.4, 13.4 Hz), 3.60 (1H, dd, *J* = 6.7, 13.4 Hz), 2.61 (3H, s), 1.55 (6H, s). LCMS (M+H)⁺ *m/z* 491 (*t* = 1.73 min.).

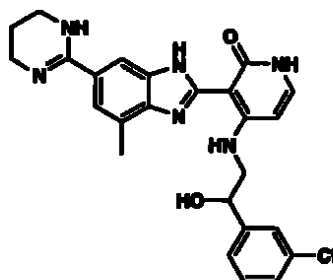
10 Example 389



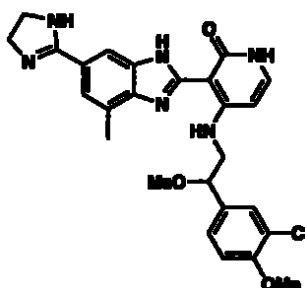
2-(2-{4-[2-(3-Chloro-phenyl)-2*R*-hydroxy-ethylamino]-2-oxo-1,2-dihydro-

pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-4,5-dihydro-1H-imidazole-4*S*-

- 15 carboxylic acid and 2-(2-{4-[2-(3-Chloro-phenyl)-2*S*-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-4,5-dihydro-1H-imidazole-4*S*-carboxylic acid: ¹H NMR (300 MHz, CD₃OD) δ 7.88 (2H, s), 7.52 (2H, s), 7.22 – 7.44 (10H, m), 6.17 (2H, d, *J* = 7.4 Hz), 5.05 (2H, m), 4.23 – 4.38 (4H, m), 3.56 – 3.72 (6H, m), 2.58 (6H, s). LCMS (M+H)⁺ *m/z* 507 (*t* = 1.64 min.).

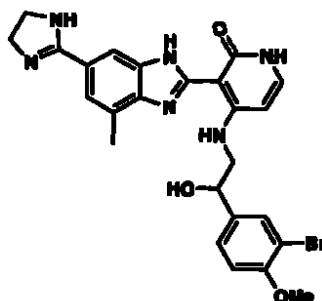
Example 390

- 5 **(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 7.90 (1H, s), 7.53 (1H, s), 7.22 – 7.47 (5H, m), 6.23 (1H, d, J = 7.6 Hz), 5.00 (1H, t, J = 6.3 Hz), 4.49 – 4.57 (1H, m), 3.60 – 3.77 (5H, m), 3.24 – 3.34 (2H, m), 2.63 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 477 (t = 1.59 min.).

10 **Example 391**

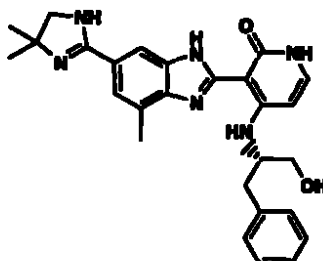
- 15 **(±)-4-[2-(3-Chloro-4-methoxy-phenyl)-2-methoxy-ethylamino]-3-[6-(4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 7.88 (1H, s), 7.46 (1H, s), 7.44 (1H, s), 7.31 (1H, d, J = 6.4 Hz), 7.28 (1H, d, J = 5.6 Hz), 7.01 (1H, d, J = 6.4 Hz), 6.19 (1H, d, J = 5.6 Hz), 4.49 (1H, dd, J = 3.4, 5.0 Hz), 4.09 (4H, s), 3.82 (3H, s), 3.36 (3H, s), 3.63 – 3.67 (2H, m), 2.62 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 507 (t = 1.72 min.).

Example 392



- 5 **(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[6-(4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one:** The title compound was prepared following hydrolysis of the benzylic chloride to the hydroxyl. ¹H NMR (400 MHz, CD₃OD) δ 7.90 (1H, s), 7.67 (1H, s), 7.48 (1H, s), 7.38 (1H, dd, *J* = 2.0, 8.5 Hz), 7.31 (1H, d, *J* = 7.6 Hz), 6.95 (1H, d, *J* = 8.5 Hz), 6.26 (1H, d, *J* = 7.6 Hz), 4.94 (1H, m), 4.10 (4H, s), 3.80 (3H, s), 3.62 – 3.74 (2H, m), 2.62
- 10 (3H, s). LCMS (M+H)⁺ *m/z* 537 (*t* = 1.49 min.).

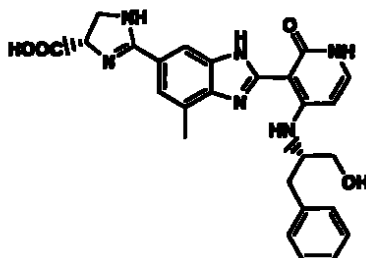
Example 393



- 15 **(S)-3-[6-(4,4-Dimethyl-4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one:** ¹H NMR (300 MHz, CD₃OD) δ 7.94 (1H, s), 7.50 (1H, s), 7.12 – 7.30 (6H, m), 6.15 (1H, dd, *J* = 7.7 Hz), 4.02 – 4.10 (1H, m), 3.85 (2H, s), 3.75 – 3.77 (2H, m), 2.96 – 3.17 (2H, m), 2.67 (3H, s), 1.56 (6H, s). LCMS (M+H)⁺ *m/z* 471 (*t* = 1.62 min.).

20

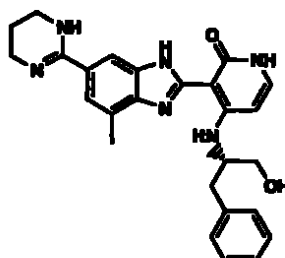
Example 394



(S)-2-(2-[4-(1S-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-
 5 3-yl]-7-methyl-3H-benzimidazol-5-yl)-4,5-dihydro-1H-imidazole-4S-carboxylic
 acid. ^1H NMR (300 MHz, CD_3OD) δ 8.03 (1H, s), 7.60 (1H, s), 7.11 – 7.29 (6H, m),
 6.15 (1H, d, $J = 7.3$ Hz), 5.07 (1H, dd, $J = 6.9, 11.8$ Hz), 4.25 – 4.41 (2H, m), 4.05 –
 4.07 (1H, m), 3.70 – 3.82 (2H, m), 3.12 (1H, dd, $J = 5.5, 13.6$ Hz), 2.95 (1H, dd, $J =$
 8.0, 13.6 Hz), 2.69 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 487 ($t = 1.35$ min.).

10

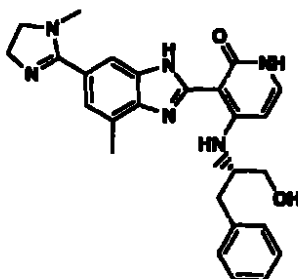
Example 395



(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6(1,4,5,6-tetrahydro-
 15 pyrimidin-2-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ^1H NMR (300 MHz,
 CD_3OD) δ 7.76 (1H, s), 7.32 (1H, s), 7.09 – 7.29 (6H, m), 6.15 (1H, d, $J = 7.6$ Hz),
 4.02 – 4.07 (1H, m), 3.71 – 3.79 (2H, m), 3.61 (4H, t, $J = 5.6$ Hz), 3.14 (1H, dd, $J =$
 5.3, 13.6 Hz), 2.95 (1H, dd, $J = 8.1, 13.6$ Hz), 2.65 (3H, s), 2.09 – 2.16 (2H, m).
 LCMS ($\text{M}+\text{H}$) $^+$ m/z 457 ($t = 1.49$ min.).

20

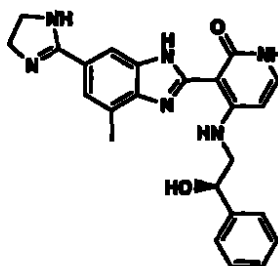
Example 396



(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-1H-benzimidazo-2-yl]-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 7.77 (1H, s), 7.10 – 7.30 (7H, m), 6.16 (1H, d, J = 7.6 Hz), 3.97 – 4.20 (5H, m), 3.73 – 3.77 (2H, m), 3.26 (3H, s), 3.15 (1H, dd, J = 5.3, 13.6 Hz), 2.96 (1H, dd, J = 8.0, 13.6 Hz), 2.68 (3H, s). LCMS (M+H)⁺ m/z 457 (t = 1.53 min.)

10

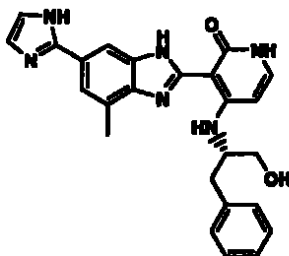
Example 397



(S)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(2-hydroxy-2-phenyl-ethylamino)-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.91 (1H, s), 7.50 (1H, s), 7.48 (2H, s), 7.24 – 7.35 (4H, m), 6.25 (1H, d, J = 7.6 Hz), 5.01 (1H, dd, J = 4.6, 7.0 Hz), 4.10 (4H, s), 3.65 – 3.76 (2H, m), 2.64 (3H, s). LCMS (M+H)⁺ m/z 429 (t = 1.48 min.).

15

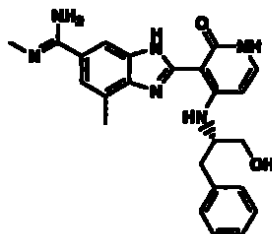
Example 398



(S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[6-(1H-imidazol-2-yl)-4-methyl-
 5 1H-benzimidazol-2-yl]-1H-pyridin-2-one: To a solution of the imidate ester (150
 mg, 0.31 mmol) in methanol (10 mL) was added aminoacetaldehyde diethyl acetal (97
 mg, 0.93 mmol). The mixture was stirred at room temperature for 14 h. The solvent
 was removed *in vacuo* and the residue was treated with 60% HClO₄ (5 mL) at room
 temperature for 14 h. The reaction mixture was then neutralized with ammonium
 10 hydroxide (conc.). The inorganic salt was filtered. The filtrate was concentrated and
 purified by prep. HPLC to yield the title compound (37 mg, 27%) as a white solid. ¹H
 NMR (300 MHz, CD₃OD) δ 7.94 (1H, narrow d, *J* = 1.3 Hz), 7.58 (2H, s), 7.53 (1H,
 narrow d, *J* = 0.6 Hz), 7.12 – 7.31 (6H, m), 6.16 (1H, d, *J* = 7.7 Hz), 4.04 – 4.08 (1H,
 m), 3.76 – 3.79 (2H, m), 3.16 (1H, dd, *J* = 5.4, 13.6 Hz), 3.97 (1H, dd, *J* = 8.1, 13.6
 15 Hz), 2.69 (3H, s). LCMS (M+H)⁺ *m/z* 441 (*t* = 1.60 min.).

General Procedure for Amidine Formation, Examples 399 - 412 (Scheme IV, 16)

Example 399

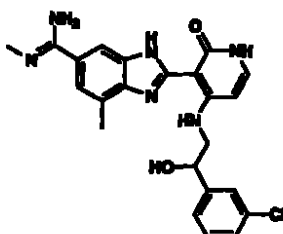


20

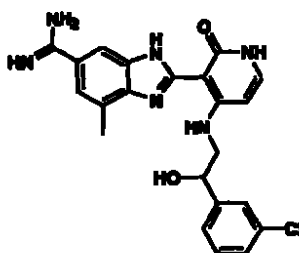
(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-
 yl]-7,*N*-dimethyl-3H-benzimidazole-5-carboxamidinium: The crude imidate ester (60
 mg, 0.135 mmol) was diluted with methanol (10 mL), then methylamine (2.0 M
 methanol solution, 0.5 mL, excess) was added to the solution. After stirring for 2 h,
 25 the reaction mixture was concentrated and purified by prep. HPLC to yield the title

compound (32 mg, 55%) as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.82 (1H, s), 7.38 (1H, s), 7.10 – 7.30 (6H, m), 6.15 (1H, $J = 7.7$ Hz), 4.03 – 4.07 (1H, m), 4.72 – 4.76 (2H, m), 3.06 – 3.18 (1H, m), 3.12 (3H, s), 2.96 (1H, dd, $J = 8.0, 13.5$ Hz), 2.67 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 431 ($t = 1.34$ min.).

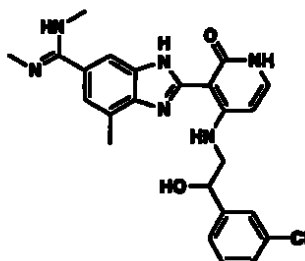
5

Example 400

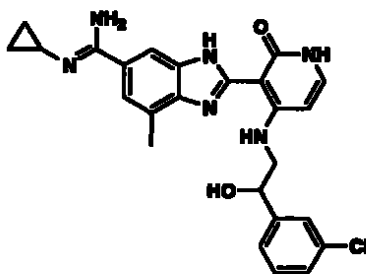
(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N-dimethyl-3H-benzimidazole-5-carboxamidine: ^1H NMR (300 MHz, CD_3OD) δ 7.81 (1H, s), 7.54 (1H, s), 7.23 – 7.54 (5H, m), 6.26 (1H, d, $J = 7.6$ Hz), 5.01 (1H, t, $J = 4.8$ Hz), 3.77 (1H, dd, $J = 4.5, 13.4$ Hz), 3.67 (1H, dd, $J = 6.6, 13.4$ Hz), 3.12 (3H, s), 2.66 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 451 ($t = 1.32$ min.).

15 **Example 401**

(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carboxamidine: ^1H NMR (300 MHz, CD_3OD) δ 7.90 (1H, s), 7.26 – 7.57 (6H, m), 6.25 (1H, d, $J = 7.6$ Hz), 5.01 (1H, t, $J = 6.4$ Hz), 3.75 (1H, dd, $J = 4.8, 13.4$ Hz), 3.66 (1H, dd, $J = 6.7, 13.4$ Hz), 2.62 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 437 ($t = 1.59$ min.).

Example 402

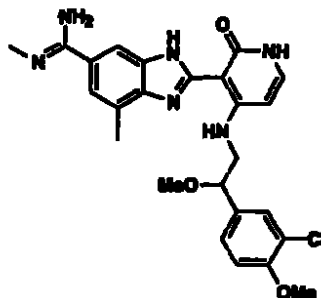
(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-
 5 3-yl}-7,N,N-trimethyl-3H-benzimidazole-5-carboxamide: ¹H NMR (300 MHz, CD₃OD) δ 7.63 (1H, s), 7.54 (1H, s), 7.18 – 7.41 (5H, m), 6.26 (1H, d, *J* = 7.6 Hz), 5.01 (1H, t, *J* = 6.3 Hz), 3.77 (1H, dd, *J* = 4.7, 13.5 Hz), 3.67 (1H, dd, *J* = 6.6, 13.5 Hz), 3.34 (6H, s), 2.66 (3H, s). LCMS (M+H)⁺ *m/z* 465 (*t* = 1.57 min.).

Example 403

(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-
 3-yl}-N-cyclopropyl-7-methyl-3H-benzimidazole-5-carboxamide: ¹H NMR (300
 15 MHz, CD₃OD) δ 7.78 (1H, s), 7.54 (1H, s), 7.22 – 7.41 (5H, m), 6.25 (1H, d, *J* = 7.6 Hz), 5.01 (1H, t, *J* = 6.4 Hz), 3.76 (1H, dd, *J* = 4.7, 13.5 Hz), 3.67 (1H, dd, *J* = 6.6, 13.5 Hz), 2.77 – 2.83 (1H, m), 2.65 (3H, s), 1.03 – 1.10 (2H, m), 0.86 – 0.92 (2H, m). LCMS (M+H)⁺ *m/z* 477 (*t* = 1.43 min.).

79

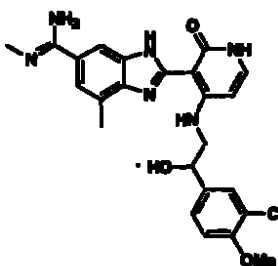
Example 404



(±)-2-{4-[2-(3-Chloro-4-methoxy-phenyl)-2-methoxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N-dimethyl-3H-benzimidazole-5-carboxamidine: ¹H NMR (300 MHz, CD₃OD) δ 7.79 (1H, narrow d, J = 1.0 Hz), 7.45 (1H, narrow d, J = 1.5 Hz), 7.38 (1H, s), 7.28 – 7.31 (2H, m), 7.02 (1H, d, J = 6.4 Hz), 6.22 (1H, d, J = 5.7 Hz), 4.52 (1H, t, J = 5.9 Hz), 3.83 (3H, s), 3.60 – 3.71 (2H, m), 3.36 (3H, s), 3.13 (3H, s), 2.65 (3H, s). LCMS (M+H)⁺ m/z 495 (t = 1.64 min.).

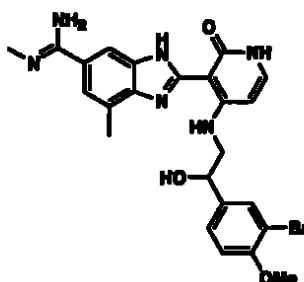
10

Example 405



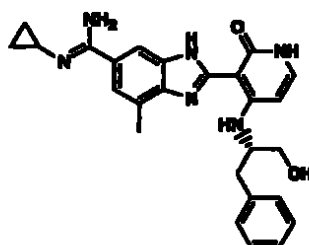
(±)-2-{4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N-dimethyl-3H-benzimidazole-5-carboxamidine: To a solution of 2-{4-[2-(3-chloro-4-methoxy-phenyl)-2-methoxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N-dimethyl-3H-benzimidazole-5-carboxamidine (40 mg, 0.08 mmol) in methanol (5 mL) was added 2 N NaOH (0.5 mL) and the reaction mixture was stirred at room temperature for 14 h. After concentration *in vacuo*, the residue was purified by prep. HPLC to yield the title compound (7.2 mg, 19%) as oil. ¹H NMR (300 MHz, CD₃OD) δ 7.78 (1H, narrow d, J = 1.6 Hz), 7.52 (1H, narrow d, J = 2.1 Hz), 7.30 – 7.36 (3H, m), 6.99 (1H, d, J = 8.5 Hz), 6.27 (1H, d, J = 7.6 Hz), 4.94 (1H, t, J = 5.9 Hz), 3.82 (3H, s), 3.68 – 3.72 (2H, m), 3.13 (3H, s), 2.63 (3H, s). LCMS (M+H)⁺ m/z 481 (t = 1.44 min.).

20

Example 406

- 5 **(±)-2-[4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamide:** ¹H NMR (400 MHz, CD₃OD) δ 7.77 (1H, s), 7.67 (1H, s), 7.29 – 7.39 (3H, m), 6.95 (1H, d, *J* = 8.4 Hz), 6.23 (1H, d, *J* = 4.4 Hz), 4.92 (1H, m), 3.80 (3H, s), 3.69 (2H, m), 3.13 (3H, s), 2.61 (3H, s). LCMS (M+H)⁺ *m/z* 525 (*t* = 1.44 min.).

10

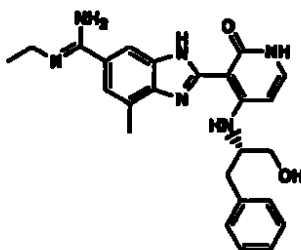
Example 407

- 15 **(S)-N-Cyclopropyl-2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxamide:** ¹H NMR (300 MHz, CD₃OD) δ 7.81 (1H, s), 7.37 (1H, s), 7.10 – 7.30 (6H, m), 6.16 (1H, d, *J* = 7.6 Hz), 4.03 – 4.08 (1H, m), 3.74 – 3.76 (2H, m), 3.15 (1H, dd, *J* = 5.3, 13.6 Hz), 2.96 (1H, dd, *J* = 8.1, 13.6 Hz), 2.78 – 2.84 (1H, m), 2.67 (3H, s), 1.03 – 1.10 (2H, m), 0.87 – 0.92 (2H, m). LCMS (M+H)⁺ *m/z* 457 (*t* = 1.51 min.).

20

6080

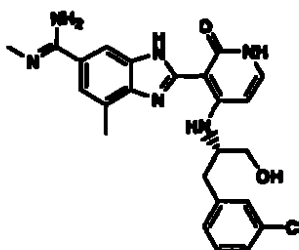
Example 408



5 (S)-N-Ethyl-2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxamide: ^1H NMR (400 MHz, CD_3OD) δ 7.82 (1H, s), 7.38 (1H, s), 7.12 – 7.30 (6H, m), 6.15 (1H, d, $J = 7.8$ Hz), 4.04 – 4.07 (1H, m), 3.75 – 3.77 (2H, m), 3.51 (2H, q, $J = 7.3$ Hz), 3.15 (1H, dd, $J = 5.4, 13.7$ Hz), 2.96 (1H, dd, $J = 8.1, 13.7$ Hz), 2.67 (3H, s), 1.40 (3H, t, $J = 7.3$ Hz). LCMS ($\text{M}+\text{H}$) $^+$ m/z 445 ($t = 1.44$ min.).

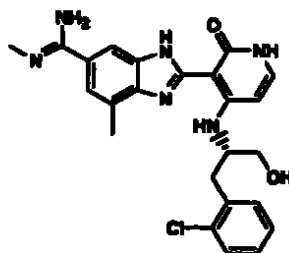
10

Example 409



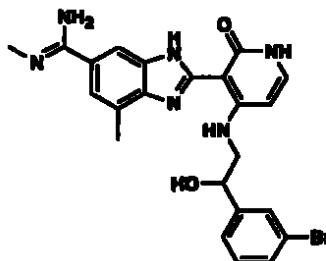
15 (S)-2-[4-[2-(3-chloro-phenyl)-1-hydroxymethyl-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamide: ^1H NMR (400 MHz, CD_3OD) δ 7.83 (1H, s), 7.38 (1H, s), 7.31 (1H, s), 7.10 – 7.24 (4H, m), 6.16 (1H, d, $J = 7.6$ Hz), 4.06 – 4.09 (1H, m), 3.72 – 3.77 (2H, m), 3.16 (3H, s), 3.15 (1H, m), 2.96 (1H, dd, $J = 8.2, 13.7$ Hz), 2.67 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 465 ($t = 1.49$ min.).

20

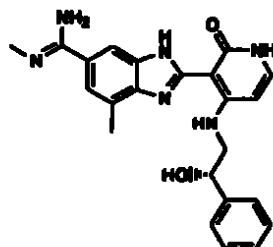
Example 410

(S)-2-{4-[2-(2-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N-dimethyl-3H-benzimidazole-5-carboxamide: ^1H NMR (400 MHz, CD_3OD) δ 7.84 (1H, s), 7.41 (1H, s), 7.32 – 7.35 (2H, m), 7.06 – 7.18 (3H, m), 6.10 (1H, d, $J = 7.5$ Hz); 4.20 – 4.24 (1H, m), 3.76 – 3.85 (2H, m), 3.30 – 3.34 (1H, m), 3.06 – 3.14 (1H, m), 3.13 (3H, s), 2.64 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 465 ($t = 1.48$ min.).

10

Example 411

(±)-2-{4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N-dimethyl-3H-benzimidazole-5-carboxamide: ^1H NMR (300 MHz, CD_3OD) δ 7.80 (1H, s), 7.69 (1H, s), 7.20 – 7.45 (5H, m), 6.25 (1H, d, $J = 7.3$ Hz), 5.00 (1H, t, $J = 5.9$ Hz), 3.64 – 3.80 (2H, m), 3.12 (3H, s), 2.66 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 495 ($t = 1.49$ min.).

Example 412

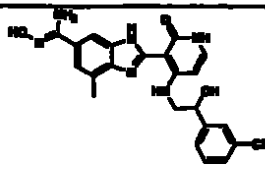
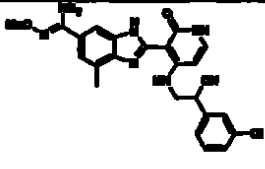
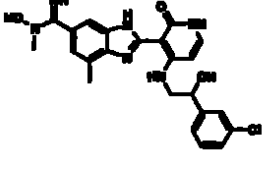
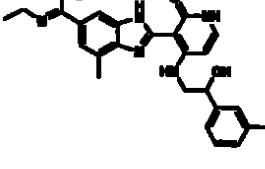
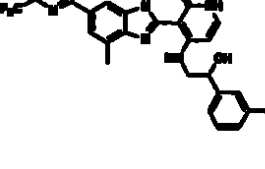
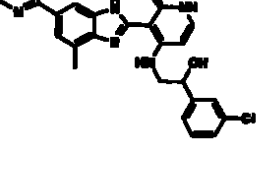
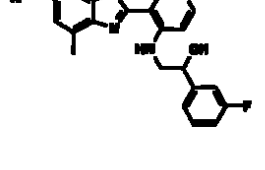
67
81

(S)-2-[4-(2-Hydroxy-2-phenylethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamide: ^1H NMR (400 MHz, CD_3OD) δ 7.78 (1H, s), 7.24 – 7.49 (7H, m), 6.21 (1H, d, $J = 7.0$ Hz), 4.00 – 5.05 (1H, m), 3.61 – 3.74 (2H, m), 3.12 (3H, s), 2.63 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 417 ($t = 1.28$ min.).

Example #	Name	Structure	T (min.)	Mass ($\text{M}+\text{H}$) $^+$ m/z
413	($\pm$)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(1-imino-1-morpholin-4-yl-methyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.55 (f)	507
414	($\pm$)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[6-(4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.49 (b)	537
415	($\pm$)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-N-(2,2-diethoxy-ethyl)-7-methyl-3H-benzimidazole-5-carboxamide		1.77 (f)	553
416	($\pm$)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.71 (f)	461
417	($\pm$)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(7'-methyl-1H, 3'H-[2,5']bibenzimidazolyl-2'-yl)-1H-pyridin-2-one		1.82 (b)	511
418	($\pm$)-Cis-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-3-(7'-methyl-3a,4,5,6,7,7a-hexahydro-		1.75 (b)	517

	1H,3'H-[2,5']bibenzimidazolyl-2'-yl)-1H-pyridin-2-one			
419	(±)- <i>Trans</i> -4-[2-(3-chlorophenyl)-2-hydroxyethylamino]-3-(7'-methyl-3a,4,5,6,7,7a-hexahydro-1H,3'H-[2,5']bibenzimidazolyl-2'-yl)-1H-pyridin-2-one		1.75 (b)	517
420	(±)-2-[4-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-N-cyclopentyl-7-methyl-3H-benzimidazole-5-carboxamidine		1.55 (b)	505
421	(±)-2-[4-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-N-cyclohexyl-7-methyl-3H-benzimidazole-5-carboxamidine		1.61 (b)	519
422	(±)-2-[4-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N-propyl-3H-benzimidazole-5-carboxamidine		1.48 (b)	479
423	(±)-2-[4-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N,N'-dipropyl-3H-benzimidazole-5-carboxamidine		1.61 (b)	521
424	(±)-2-[4-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-N-isopropyl-7-methyl-3H-benzimidazole-5-carboxamidine		1.41 (b)	479

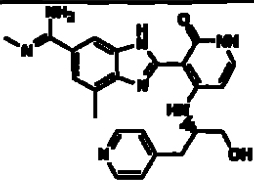
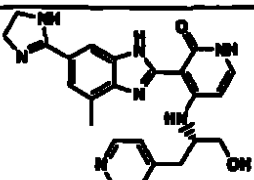
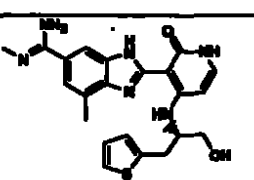
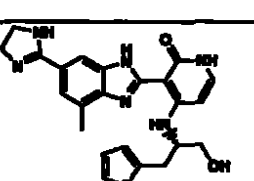
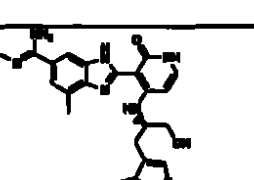
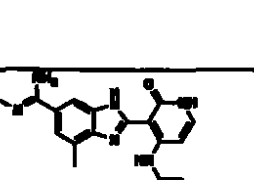
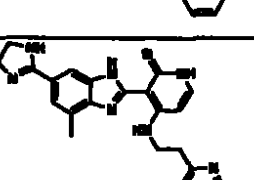
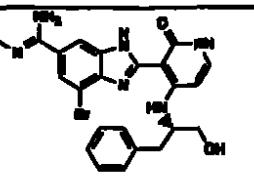
425	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N-(2-morpholin-4-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.27 (b)	550
426	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N,N'-bis-(2-morpholin-4-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.22 (b)	663
427	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-N-(2-hydroxy-ethyl)-7-methyl-3H-benzimidazole-5-carboxamidine		1.38 (b)	481
428	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(5-methyl-1H-imidazol-2-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.62 (b)	475
429	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-4-methyl-1H-benzimidazole-6-carboxamidic acid hydrazide		1.44 (f)	452
430	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-4-methyl-1H-benzimidazole-6-carboxamidic acid N-formylhydrazide		1.58 (f)	480
431	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(4H-[1,2,4]triazol-3-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.82 (f)	462

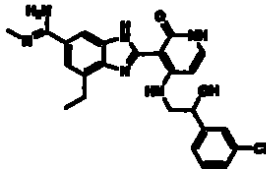
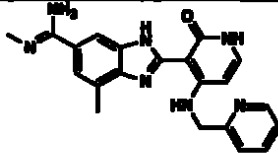
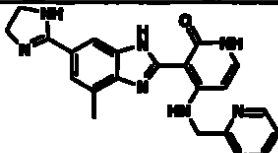
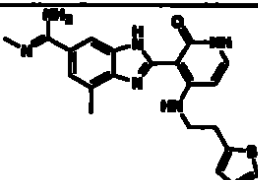
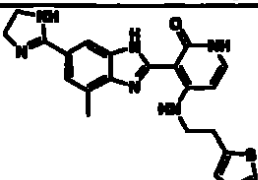
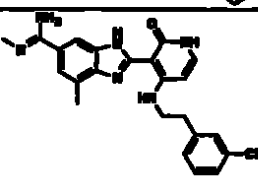
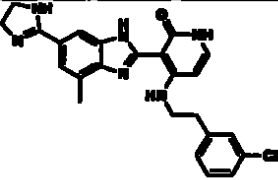
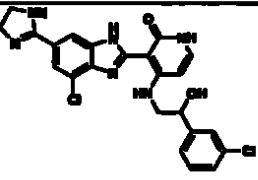
432	(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-N-hydroxy-7-methyl-3H-benzimidazole-5-carboxamidine		1.34 (f)	453
433	(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-N-methoxy-7-methyl-3H-benzimidazole-5-carboxamidine		1.41 (f)	467
434	(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-N-hydroxy-7,N-dimethyl-3H-benzimidazole-5-carboxamidine		1.39 (f)	467
435	(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-N-ethyl-7-methyl-3H-benzimidazole-5-carboxamidine		1.62 (f)	465
436	(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-N-(2,2,2-trifluoroethyl)-3H-benzimidazole-5-carboxamidine		1.75 (f)	519
437	(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N,N'-trimethyl-3H-benzimidazole-5-carboxamidine		1.58 (f)	465
438	(±)-2-{4-[2-(3-Fluoro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7,N-dimethyl-3H-benzimidazole-5-carboxamidine		1.28 (b)	435

b3
83

439	(±)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-fluoro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.46 (b)	447
440	(±)-3-[6-(5,5-Dimethyl-4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-fluoro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.59 (b)	475
441	(S)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-phenyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		2.90 (b)	505
442	(S)-3-[4-Bromo-6-(4,5-dihydro-1H-imidazol-2-yl)-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.57 (b)	507
443	(±)-[2-Chloro-4-(1-hydroxy-2-[3-[4-methyl-6-(N-methylcarbamimidoyl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl)-phenyl]-carbamic acid isobutyl ester		1.64 (b)	566
444	(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N-(2-morpholin-4-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.33 (b)	530
445	(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N-(2-thiophen-2-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.62 (b)	527
446	(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N-(2-pyridin-2-yl-ethyl)-3H-benzimidazole-5-		1.40 (b)	522

	carboxamidine			
447	(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N-(2-pyridin-3-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.37 (b)	522
448	(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N-(2-pyridin-4-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.25 (b)	522
449	(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N,N'-bis-(2-pyridin-3-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.24 (b)	627
450	(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-N,N'-bis-(2-pyridin-4-yl-ethyl)-3H-benzimidazole-5-carboxamidine		1.16 (b)	627
451	(S)-4-[2-(2-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-[6-(4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.53 (b)	477
452	(S)-2-[4-(1-Hydroxymethyl-2-pyridin-3-yl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamidine		0.80 (b)	432
453	(S)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-pyridin-3-yl-ethylamino)-1H-pyridin-2-one		0.98 (b)	444

454	(S)-2-[4-(1-Hydroxymethyl-2-pyridin-4-yl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamide		0.73 (b)	432
455	(S)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-pyridin-4-yl-ethylamino)-1H-pyridin-2-one		0.98 (b)	444
456	(S)-2-[4-(1-Hydroxymethyl-2-thiophen-2-yl-ethylamino)-2-oxo-1,2-dihydro-pyridin-4-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamide		1.24 (b)	437
457	(S)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-thiophen-2-yl-ethylamino)-1H-pyridin-2-one		1.46 (b)	449
458	(S)-2-[4-(2-Benzo[b]thiophen-3-yl-1-hydroxymethyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamide		1.47 (b)	487
459	7,N-Dimethyl-2-[2-oxo-4-(2-pyridin-2-yl-ethylamino)-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxamide		0.86 (b)	402
460	3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(2-pyridin-2-yl-ethylamino)-1H-pyridin-2-one		0.91 (b)	414
461	(S)-7-Bromo-2-[4(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-N-methyl-3H-benzimidazole-5-carboxamide		1.47 (b)	495

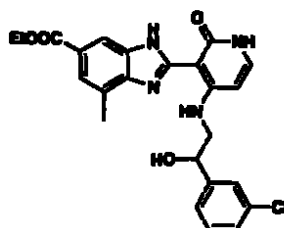
462	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-ethyl-N-methyl-3H-benzimidazole-5-carboxamidine		1.51 (d)	465
463	7,N-Dimethyl-2-[2-oxo-4-(2-pyridin-2-ylmethylamino)-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxamidine		0.98 (b)	388
464	3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[(pyridin-2-ylmethyl)-amino]-1H-pyridin-2-one		1.07 (b)	400
465	7,N-Dimethyl-2-[2-oxo-4-(2-thiophen-2-yl-ethylamino)-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxamidine		1.53 (b)	407
466	3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(2-thiophen-2-yl-ethylamino)-1H-pyridin-2-one		1.62 (b)	419
467	(±)-2-[4-[2-(3-Chloro-phenyl)-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7,N-dimethyl-3H-benzimidazole-5-carboxamidine		1.57 (b)	435
468	(±)-4-[2-(3-Chloro-phenyl)-ethylamino]-3-[6-(4,5-dihydro-1H-imidazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.66 (b)	447
469	(±)-3-[4-Chloro-6-(4,5-dihydro-1H-imidazol-2-yl)-1H-benzimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.40 (d)	483

85

470	(±)-3-[4-Chloro-6-(5,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-1H-benzimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one		1.52 (d)	511
471	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(5,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-4-ethyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.57 (d)	505
472	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4,5-dihydro-1H-imidazol-2-yl)-4-ethyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.49 (d)	477
473	(S)-3-[6-(4,5-Dihydro-1H-imidazol-2-yl)-4-ethyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one		1.47 (d)	457
474	(S)-7-Ethyl-2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-N-methyl-3H-benzimidazole-5-carboxamidine		1.42 (d)	445

Amide Formation

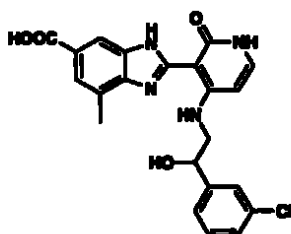
Intermediate Synthesis



5

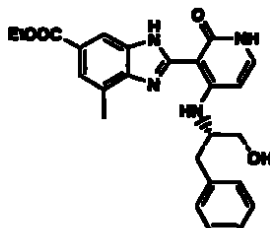
(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid ethyl ester: A solution of (±)-2-{4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-

7-methyl-3H-benzimidazole-5-carboximidic acid ethyl ester (400 mg, 0.90 mmol) was diluted with 2 N HCl (20 mL) solution and the mixture was allowed to stir at room temperature for 14 h. After concentration to dryness, the crude product (419 mg, 100%) was used for the next step without purification. Small amount was purified by prep. HPLC to yield the title compound. ¹H NMR (300 MHz, CD₃OD) δ 8.11 (1H, s), 7.74 (1H, s), 7.25 – 7.54 (5H, m), 6.25 (1H, d, *J* = 7.6 Hz), 4.99 (1H, t, *J* = 7.2 Hz), 4.38 (2H, q, *J* = 7.1 Hz), 3.61 – 3.76 (2H, m), 2.61 (3H, s), 1.42 (3H, q, *J* = 7.1 Hz). LCMS (M+H)⁺ *m/z* 467 (*t* = 2.23 min.).



(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid: The ethyl ester (419 mg, 0.90 mmol) obtained above was diluted with methanol (15 mL) and water (5 mL) followed by addition of sodium hydroxide (180 mg, 4.5 mmol). The mixture was stirred at room temperature for 14 h. After removal of methanol, the residue was neutralized with 2 N HCl solution. The resulting slurry was filtered and washed with ice-cold water. The solid was collected after drying over high vacuum. The crude product (395 mg, 100% yield, 80% pure) was used for the next step without further purification. ¹NMR (300 MHz, CD₃OD) δ 8.20 (1H, s), 7.92 (1H, s), 7.27 – 7.47 (5H, m), 6.27 (1H, d, *J* = 7.6 Hz), 4.85 (1H, m), 3.63 (2H, m), 2.67 (3H, s). LCMS (M+H)⁺ *m/z* 439 (*t* = 1.88 min.).

Example 475

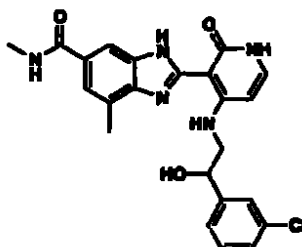


b6
86

(S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid ethyl ester: The imidate ester (30 mg, 0.067 mmol) was dilute with methanol (10 mL) and two drops of water was added. The reaction mixture was stirred at room temperature for 20 h. After concentration *in vacuo*, the residue was purified by prep. HPLC to yield the title compound (18.2 mg, 61%) as a white solid. ¹H NMR (300 MHz, CD₃OD) δ 7.74 (1H, s), 7.11 – 7.30 (7H, m), 6.10 (1H, d, *J* = 6.9 Hz), 4.37 (2H, q, *J* = 6.6 Hz), 4.02 (1H, broad s), 3.69 – 3.81 (2H, m), 3.10 (1H, dd, *J* = 4.8, 13.5 Hz), 2.93 (1H, dd, *J* = 7.8, 13.5 Hz), 2.62 (3H, s), 1.41 (3H, t, *J* = 6.6 Hz). LCMS (M+H)⁺ *m/z* 447 (*t* = 1.95 min.).

Preparation of Amides Starting from (±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid, Examples 476 - 504, Scheme IV, 15

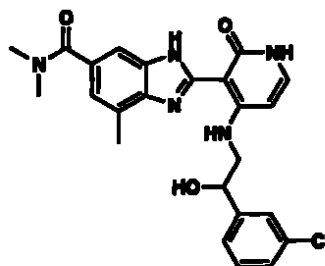
Example 476



(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid methylamide: To a solution of the acid (50 mg, 0.11 mmol) in DMF (5 mL) was added diphenylphosphoryl azide (38 mg, 0.14 mmol). The mixture was allowed to stir for 5 min. Then methylamine (2.0 M solution in THF)(0.11 mL, 0.22 mmol) was added. The mixture was stirred at room temperature for 14 h. After removal of DMF with high vacuum, the residue was purified by prep. HPLC to yield the title compound (18 mg, 36%) as a white solid. ¹H NMR (300 MHz, CD₃OD) δ 7.89 (1H, s), 7.18 – 7.53 (6H, m), 6.23 (1H, d, *J* = 7.6

Hz), 4.98 (1H, m), 3.70 (1H, dd, $J = 4.7, 13.5$ Hz), 3.61 (1H, dd, $J = 7.0, 13.5$ Hz), 2.94 (3H, s), 2.61 (3H, s). LCMS $(M+H)^+$ m/z 452 ($t = 1.57$ min.).

Example 477

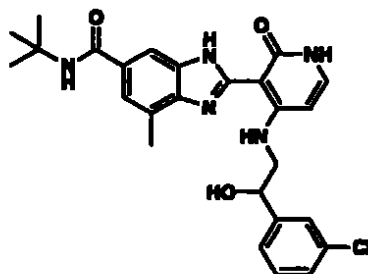


5

(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid dimethylamide: ^1H NMR (300 MHz, CD_3OD) δ 7.52 (1H, s), 7.24 – 7.40 (5H, m), 7.15 (1H, s), 6.25 (1H, d, $J = 7.6$ Hz), 4.98 (1H, dd, $J = 5.0, 6.9$ Hz), 3.70 (1H, dd, $J = 4.8, 13.5$ Hz), 3.62 (1H, dd, $J = 7.0, 13.5$ Hz), 3.3 (3H, s), 3.08 (3H, s), 2.62 (3H, s). LCMS $(M+H)^+$ m/z 466 ($t = 1.84$ min.).

10

Example 478



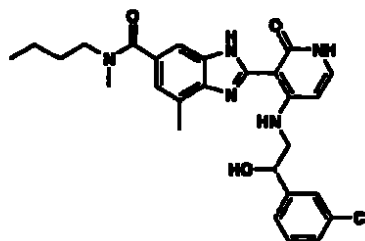
15

(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid *tert*-butylamide: ^1H NMR (300 MHz, CD_3OD) δ 7.82 (1H, s), 7.53 (1H, s), 7.48 (1H, s), 7.24 – 7.40 (4H, m), 6.25 (1H, d, $J = 7.6$ Hz), 5.00 (1H, m), 3.64 – 3.70 (2H, m), 2.62 (3H, s), 1.49 (9H, s). LCMS $(M+H)^+$ m/z 494 ($t = 1.79$ min.).

20

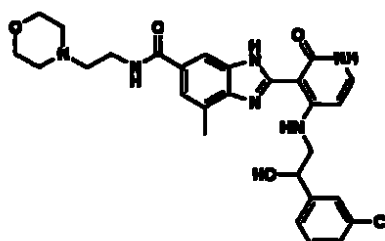
6787

Example 479



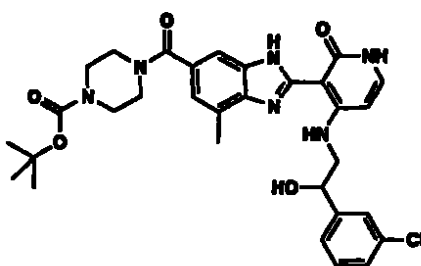
(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-
 5 3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid butyl-methyl-amide: ^1H NMR
 (300 MHz, CD_3OD) δ 7.51 (1H, s), 7.48 (1H, s), 7.24 – 7.39 (4H, m), 7.13 (1H, s),
 6.22 (1H, d, $J = 7.6$ Hz), 4.95 (1H, m), 3.55 – 3.70 (3H, m), 3.34 (1H, m), 3.05 (3H,
 s), 2.62 (3H, s), 0.79 – 1.69 (7H, m). LCMS ($\text{M}+\text{H}$) $^+$ m/z 508 ($t = 1.88$ min.).

10 Example 480



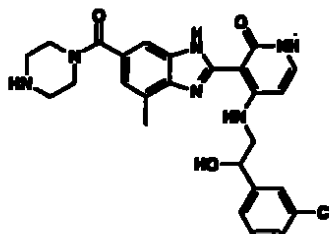
(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-
 3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid (2-morpholine-4-yl-ethyl)-
 15 amide: ^1H NMR (300 MHz, CD_3OD) δ 7.58 (1H, s), 7.52 (1H, s), 7.05 – 7.42 (5H,
 m), 6.22 (1H, d, $J = 7.6$ Hz), 4.97 (1H, dd, $J = 4.9, 6.7$ Hz), 2.60 – 4.07 (14H, m),
 2.61 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 551 ($t = 1.49$ min.).

Example 481



(±)-4-[1-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl)-methanoyl]-piperazine-1-carboxylic acid *tert*-butyl ester: ¹H NMR (300 MHz, CD₃OD) δ 7.52 (1H, s), 7.50 (1H, s), 7.24 – 7.38 (4H, m), 7.18 (1H, m), 6.22 (1H, d, *J* = 7.6 Hz), 4.97 (1H, m),
 5 3.49 – 3.69 (10H, m), 2.62 (3H, s), 1.47 (9H, s). LCMS (M+H)⁺ *m/z* 607 (*t* = 1.90 min.).

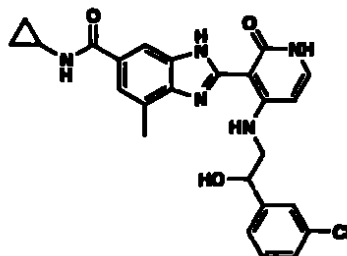
Example 482



10

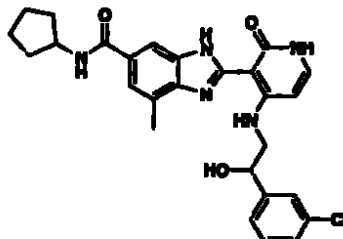
(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(1-piperazin-1-yl-methanoyl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: To a solution of (±)-4-[1-(2-{4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl)-methanoyl]-piperazine-1-carboxylic acid *tert*-butyl
 15 ester (40 mg, 0.06 mmol) in methanol (5 mL) was added 4.0 M HCl dioxane solution (0.1 mL, excess). The reaction mixture was stirred at room temperature for 14 h. After concentration, the residue was purified by prep. HPLC to give the title compound (16 mg, 63%) as a white foam. ¹H NMR (300 MHz, CD₃OD) δ 7.56 (1H, s), 7.53 (1H, s), 7.23 – 7.41 (4H, m), 7.17 (1H, m), 6.26 (1H, d, *J* = 7.6 Hz), 4.99 (1H, dd, *J* = 4.7, 6.4
 20 Hz), 3.91 (4H, broad s), 3.74 (1H, dd, *J* = 4.7, 13.5 Hz), 3.65 (1H, dd, *J* = 6.4, 13.5 Hz), 3.31 (4H, broad s), 2.63 (3H, s). LCMS (M+H)⁺ *m/z* 507 (*t* = 1.38 min.).

Example 483



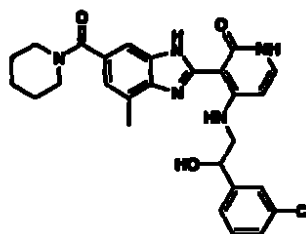
25

(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid cyclopropylamide: ¹H NMR (300 MHz, CD₃OD) δ 7.80 (1H, s), 7.21 – 7.53 (6H, m), 6.22 (1H, d, *J* = 7.6 Hz), 4.99 (1H, t, *J* = 6.4 Hz), 3.59 – 3.76 (2H, m), 2.83 – 2.90 (1H, m), 2.60 (3H, s), 0.81 – 0.89 (2H, m), 0.64 – 0.73 (2H, m). LCMS (M+H)⁺ *m/z* 478 (*t* = 1.60 min.).

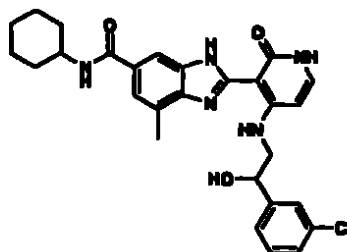
Example 484

(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid cyclopentylamide: ¹H NMR (300 MHz, CD₃OD) δ 7.97 (1H, s), 7.16 – 7.60 (6H, m), 6.22 (1H, d, *J* = 7.6 Hz), 4.35 (1H, m), 3.58 – 3.68 (2H, m), 2.62 (3H, s), 1.29 – 2.07 (9H, m). LCMS (M+H)⁺ *m/z* 506 (*t* = 1.86 min.).

15

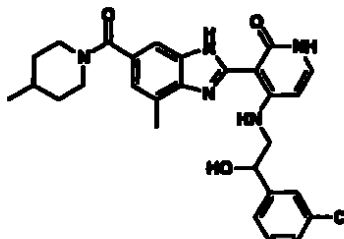
Example 485

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(1-piperidin-1-yl-methanoyl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 7.53 (1H, s), 7.46 (1H, s), 7.18 – 7.41 (4H, m), 7.07 (1H, s), 6.23 (1H, d, *J* = 7.6 Hz), 4.98 (1H, dd, *J* = 4.8, 6.6 Hz), 3.60 – 3.74 (5H, m), 3.18 – 3.24 (1H, m), 2.60 (3H, m), 1.43 – 1.7 (6H, m). LCMS (M+H)⁺ *m/z* 506 (*t* = 1.78 min.).

Example 486

(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-
 5 3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid cyclohexylamide: ¹H NMR
 (300 MHz, CD₃OD) δ 7.88 (1H, s), 7.54 (1H, s), 7.52 (1H, s), 7.16 – 7.40 (4H, m),
 6.22 (1H, *J* = 7.6 Hz), 4.97 (1H, dd, *J* = 4.7, 6.9 Hz), 3.89 (H, m), 3.69 (1H, dd, *J* =
 4.7, 13.5 Hz), 3.61 (1H, dd, *J* = 6.9, 13.5 Hz), 2.61 (3H, s), 1.19 – 2.00 (10H, m).
 LCMS (M+H)⁺ *m/z* 520 (*t* = 1.93 min.).

10

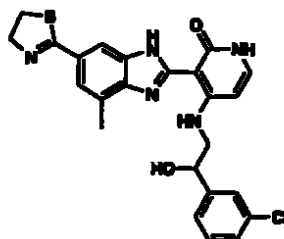
Example 487

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[1-(4-methyl-
 15 piperidin-1-yl)-methanoyl]-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR
 (300 MHz, CD₃OD) δ 7.51 (1H, s), 7.49 (1H, s), 7.21 – 7.39 (4H, m), 7.14 (1H, s),
 6.24 (1H, d, *J* = 7.6 Hz), 4.96 (1H, dd, *J* = 4.7, 7.0 Hz), 3.68 (1H, dd, *J* = 4.7, 13.6
 Hz), 3.60 (1H, dd, *J* = 7.0, 13.6 Hz), 2.62 (3H, s), 1.93 – 1.72 (9H, m), 1.00 (3H, d, *J*
 = 6.3 Hz). LCMS (M+H)⁺ *m/z* 520 (*t* = 1.97 min.).

20

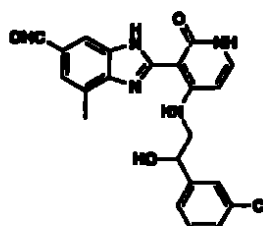
b
89

Example 488



- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4,5-dihydro-thiazol-2-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: To a solution of (±)-2-[4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile (100 mg, 0.24 mmol) in methanol (20 mL) was added 2-aminoethanethiol hydrochloride (41 mg, 0.36 mmol) and triethylamine (0.1 mL, excess). The reaction mixture was heated to reflux for 14 h and cooled to room temperature. After concentration, the residue was purified by prep. HPLC to yield the title compound (76 mg, 66%) as a yellow solid. ¹H NMR (300 MHz, CD₃OD) δ 8.10 (1H, s), 7.71 (1H, s), 7.66 (1H, s), 7.25 – 7.53 (4H, m), 6.33 (1H, d, *J* = 7.6 Hz), 5.01 (1H, dd, *J* = 4.2, 7.0 Hz), 4.58 (2H, t, *J* = 8.6 Hz), 3.91 (2H, t, *J* = 8.6 Hz), 3.73 (1H, dd, *J* = 4.2, 13.7 Hz), 3.63 (1H, dd, *J* = 7.0, 13.7 Hz), 2.64 (3H, s).
- LCMS (M+H)⁺ *m/z* 480 (*t* = 1.70 min.).

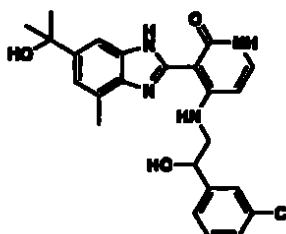
Example 489



- (±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbaldehyde: To a suspension of (±)-2-[4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile (76 mg, 0.18 mmol) in toluene (anhydrous, 20 mL) was added diisobutylaluminium (1.4 M toluene solution) (0.65 mL, 0.97 mmol) at -78°C under nitrogen. The mixture was stirred at -78°C for 6 h. Ethyl acetate (1 mL) was then added followed by water (0.5 mL). The mixture was stirred at room

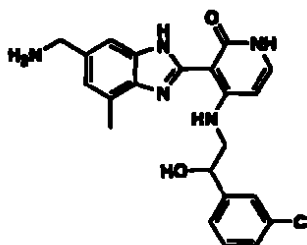
temperature for 20 min. The mixture was then passed through a pad of celite and the filtrate was concentrated. The crude product was purified by prep. HPLC to yield the title compound (4 mg, 2.5%) as a brown solid. ¹H NMR (300 MHz, CD₃OD) δ 7.65 (1H, s), 7.57 (1H, s), 7.24 – 7.50 (5H, m), 6.26 (1H, d, *J* = 7.6 Hz), 5.49 (1H, s), 4.96 (1H, m), 3.53 – 3.79 (2H, m), 2.62 (3H, s). LCMS (M+H)⁺ *m/z* 423 (*t* = 1.79 min.).

Example 490



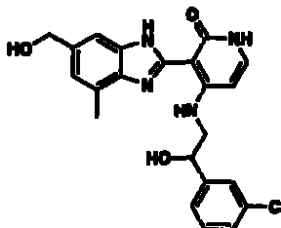
(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(1-hydroxy-1-methyl-ethyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: To a solution of (±)-2-{4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carboxylic acid ethyl ester (40 mg, 0.08 mmol) in THF (5 mL) was added methyllithium (1.4 M THF solution, 0.57 mL, 0.8 mmol) at -78°C under nitrogen. The reaction mixture was gradually warmed to room temperature overnight. After quenching with water, the mixture was partitioned between ethyl acetate and water. The organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by prep HPLC to yield the title compound (13 mg, 36%) as a colorless oil. ¹H NMR (300 MHz, CD₃OD) δ 7.66 (1H, s), 7.47 (1H, s), 7.26 – 7.41 (5H, m), 6.26 (1H, d, *J* = 7.6 Hz), 4.92 (1H, m), 3.54 – 3.61 (2H, m), 2.62 (3H, s), 1.60 (6H, s). LCMS (M+H)⁺ *m/z* 453 (*t* = 1.46 min.).

Example 491

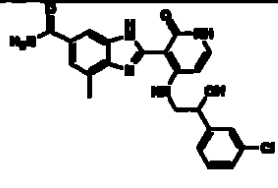
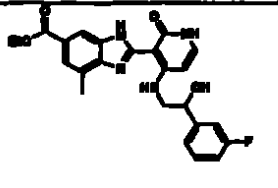
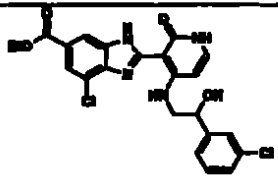
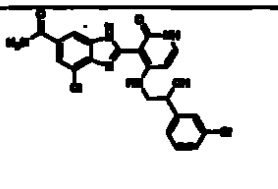
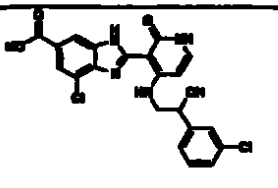
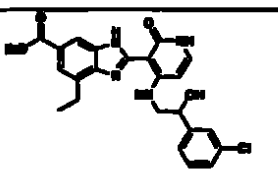
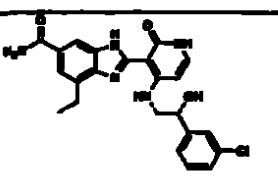


(±)-3-(6-Aminomethyl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one: To a solution of (±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid amide (20 mg, 0.046 mmol) in THF (1 mL) was
5 added borane-tetrahydrofuran complex (1 M solution) (0.45 mL, 0.45 mmol). The reaction mixture was stirred at room temperature for 10 h and quenched with acetic acid (2 drops). After removal of most solvent, the residue was extracted with EtOAc, washed with brine, dried over Na₂SO₄. After concentration, the crude product was purified by prep. HPLC to yield the title compound (11.5 mg, 60%). ¹H NMR (400
10 MHz, CD₃OD) δ 7.53 (1H, s), 7.50 (1H, s), 7.39 (1H, d, *J* = 7.5 Hz), 7.24 – 7.32 (3H, m), 7.13 (1H, s), 6.26 (1H, d, *J* = 7.5 Hz), 4.99 (1H, dd, *J* = 4.8, 6.8 Hz), 4.19 (2H, s), 3.72 (1H, dd, *J* = 4.8, 13.6 Hz), 3.64 (1H, dd, *J* = 6.8, 13.6 Hz), 2.62 (3H, s). LCMS (M+H)⁺ *m/z* 424 (*t* = 2.10 min.).

15 **Example 492**



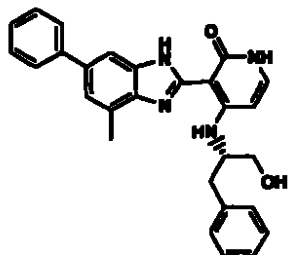
(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-hydroxymethyl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: To a solution of (±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxylic
20 acid ethyl ester (25 mg, 0.054 mmol) in methanol (2 mL) and acetic acid (1 mL) was added NaBH₄ (10 mg, 0.27 mmol) at -20°C. The reaction mixture was stirred at -20°C for 30 min. and quenched with *isopropanol* (5 drops). After removal of most solvent, the residue was extracted with EtOAc, washed with water and brine, dried over Na₂SO₄. After
25 concentration, the crude product was purified by prep. HPLC to yield the title compound (18 mg, 62%). ¹H NMR (300 MHz, CD₃OD) δ 7.50 (1H, s), 7.48 (1H, s), 7.25 – 7.38 (4H, m), 7.22 (1H, s), 6.25 (1H, d, *J* = 7.6 Hz), 4.89 – 4.94 (1H, m), 4.76 (2H, s), 3.51 – 3.62 (2H, m), 2.62 (3H, s).
LCMS (M+H)⁺ *m/z* 425 (*t* = 1.64 min.).

Example #	Name	BMS-#	T (min)	Mass (M+H) ⁺ (m/z)
493	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid amide		1.68 (f)	437
494	(±)-2-[4-[2-(3-Fluoro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid ethyl ester		1.90 (b)	451
495	(±)-7-Chloro-2-[4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxylic acid ethyl ester		2.06 (d)	487
496	(±)-7-Chloro-2-[4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxylic acid amide		1.54 (d)	458
497	(±)-7-Chloro-2-[4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxylic acid		1.69 (d)	459
498	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-ethyl-3H-benzimidazole-5-carboxylic acid ethyl ester		1.98 (d)	481
499	(±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-ethyl-3H-benzimidazole-5-carboxylic acid amide		1.51 (d)	452

500	(S)-7-Bromo-2-[4-(1-hydroxymethyl-2-phenylethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carboxylic acid ethyl ester		2.06 (b)	511
501	(±)-2-[4-[2-(3-Bromophenyl)-2-hydroxyethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid ethyl ester		1.99 (b)	511
502	(S)-2-[4-[2-(2-Chlorophenyl)-1-hydroxymethyl-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid ethyl ester		1.89 (b)	481
503	(S)-2-[4-(2-Hydroxy-2-phenylethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carboxylic acid ethyl ester		1.84 (b)	433
504	(±)-4-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(1H-tetrazol-5-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.92 (f)	463

General Procedure for Suzuki couplings, Example 505 -509 (Scheme V, 18)

Example 505

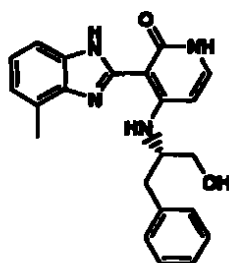


- 5 (S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-phenyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: To a solution of (S)-4-(1-benzyl-2-trityloxy-ethylamino)-3-[6-bromo-4-methyl-1H-benzimidazole-2-yl]-1H-pyridin-2-one (50 mg, 0.072 mmol), phenylboronic acid (13 mg, 0.11 mmol), and 2 M K₂CO₃ (0.108 mL, 0.22 mmol) in THF (5 mL) was added Pd(PPh₃)₄ (8.3 mg, 0.007 mmol). The mixture was heated to
- 10 reflux 14 h. Upon cooling, the reaction mixture was diluted with CH₂Cl₂, washed with

saturated NaHCO_3 , dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was used for the next step without purification. LCMS $(\text{M}+\text{H})^+$ m/z 693 ($t = 2.82$ min.). The crude product was treated with 4 N HCl dioxane solution (5 mL) at room

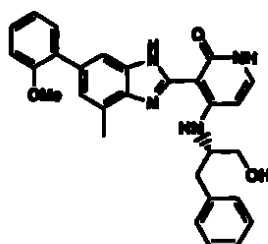
- 5 HPLC to yield the title compound (17 mg, 34%) as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.13 – 7.67 (13H, m), 6.15 (1H, d, $J = 7.4$ Hz), 3.99 – 4.11 (1H, m), 3.74 – 3.77 (2H, m), 3.16 (1H, dd, $J = 5.4, 13.6$ Hz), 2.97 (1H, dd, $J = 7.8, 13.6$ Hz), 2.69 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 451 ($t = 2.04$ min.).

10 Example 506



- (S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (300 MHz, CD_3OD) δ 6.98 – 7.46 (9H, m), 6.15 (1H, d, $J = 7.5$ Hz), 3.99 – 4.04 (1H, m), 3.75 (2H, d, $J = 5.1$ Hz), 3.16 (1H, dd, $J = 5.1, 13.6$ Hz), 2.95 (1H, dd, $J = 8.1, 13.6$ Hz), 2.61 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 375 ($t = 1.72$ min.).

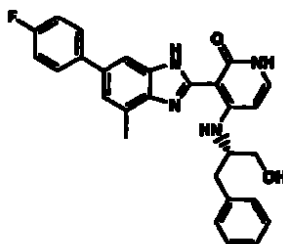
Example 507



- 20 (S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-[6-(2-methoxy-phenyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ^1H NMR (300 MHz, CD_3OD) δ 6.99 – 7.59 (12H, m), 6.16 (1H, d, $J = 7.5$ Hz), 4.04 (1H, m), 3.81 (3H, s), 3.76 (2H, d, $J = 4.1$ Hz), 2.96 – 3.20 (2H, m), 2.66 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 481 ($t = 2.00$ min.).

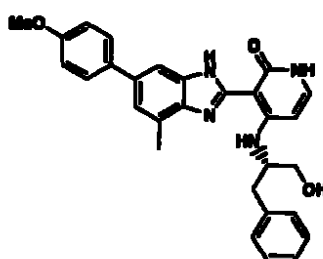
25

Example 508



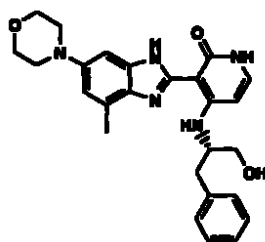
(S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-[6-(4-fluoro-phenyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 7.10 – 7.66 (12H, m), 6.13 (1H, d, *J* = 7.6 Hz), 3.99 – 4.04 (1H, m), 3.76 (2H, d, *J* = 5.0 Hz), 3.16 (1H, dd, *J* = 5.0, 13.6 Hz), 2.96 (1H, dd, *J* = 8.1, 13.6 Hz), 2.65 (3H, s). LCMS (M+H)⁺ *m/z* 469 (*t* = 2.07 min.).

10 Example 509



(S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-[6-(4-methoxy-phenyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 6.97 – 7.65 (12H, m), 6.14 (1H, d, *J* = 7.6 Hz), 4.00 – 4.04 (1H, m), 3.83 (3H, s), 3.76 (2H, d, *J* = 5.0 Hz), 2.95 – 3.19 (2H, m), 2.67 (3H, s). LCMS (M+H)⁺ *m/z* 481 (*t* = 2.01 min.).

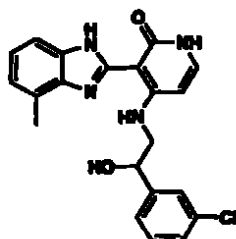
General Procedure for Buchwald couplings, Examples 510 - 516 Scheme V, 19
Example 510



20

(*S*)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: A mixture of (*S*)-4-(1-benzyl-2-trityloxy-ethylamino)-3-[6-bromo-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one (150 mg, 0.216 mmol), morpholine (28.2 mg, 0.324 mmol), palladium acetate (2.4 mg, 0.01 mmol), tri-*tert*-butylphosphine (4.4 mg, 0.02 mmol), and sodium *tert*-butoxide (104 mg, 1.08 mmol) in toluene (5 mL) was heated to 100°C for 14 h under nitrogen. The reaction mixture was cooled to room temperature and diluted with EtOAc. After extraction, the combined organic layers were washed with water, brine, dried over Na₂SO₄. Concentration gave a brownish residue, which was treated with 4 N HCl dioxane solution (3 mL) at room temperature for 6 h. After removal of the solvent, the residue was purified by prep. HPLC to yield the title compound (18 mg, 18%). ¹H NMR (400 MHz, CD₃OD) δ 7.59 (1H, s), 7.12 – 7.28 (7H, m), 6.12 (1H, d, *J* = 7.6 Hz), 4.01 – 4.08 (5H, m), 3.76 (1H, dd, *J* = 4.8, 11.1 Hz), 3.71 (1H, dd, *J* = 5.2, 11.1 Hz), 3.32 – 3.10 (4H, m), 3.09 (1H, dd, *J* = 5.6, 13.7 Hz), 2.92 (1H, dd, *J* = 8.0, 13.7 Hz), 2.65 (3H, s). LCMS (M+H)⁺ *m/z* 460 (*t* = 1.30 min.).

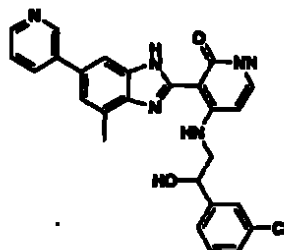
Example 511



(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (300 MHz, CD₃OD) δ 7.17 – 7.64 (8H, m), 6.23 (1H, d, *J* = 10.2 Hz), 4.94 (1H, m), 3.61 (1H, dd, *J* = 4.8, 13.8 Hz), 3.54 (1H, dd, *J* = 7.4, 13.8 Hz), 2.61 (3H, s). LCMS (M+H)⁺ *m/z* 395 (*t* = 1.65 min.).

93

Example 512



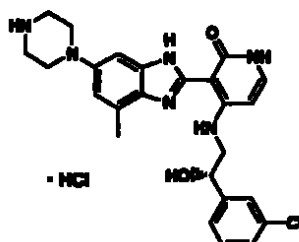
(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-pyridin-3-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (300 MHz, CD_3OD) δ 9.14 (1H, s), 8.88 (1H, d, $J = 8.2$ Hz), 8.72 (1H, d, $J = 5.4$ Hz), 8.08 (1H, dd, $J = 5.8, 8.2$ Hz), 7.82 (1H, s), 7.56 (1H, s), 7.24 – 7.45 (5H, m), 6.26 (1H, d, $J = 7.6$ Hz), 5.02 (1H, dd, $J = 5.0, 6.5$ Hz), 3.77 (1H, dd, $J = 5.0, 13.5$ Hz), 3.68 (1H, dd, $J = 6.5, 13.5$ Hz), 2.68 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 472 ($t = 1.66$ min.).

10

Example #	Name	Structure	T (min)	Mass ($\text{M}+\text{H}$) $^+$ m/z
513	(±)-3-(6-Bromo-4-methyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]1H-pyridin-2-one		2.08 (f)	473
514	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4-methoxy-phenyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one		1.96 (f)	501
515	(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.65 (f)	395
516	(S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-piperidin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one		1.39 (b)	458

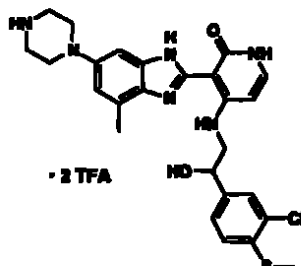
The following examples 517-519 were prepared according to Schemes VII and III.

5 **Example 517**



(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃OD) δ 7.54 (brs, 1H), 7.40 – 7.20 (m, 4H), 7.03 (brs, 1H), 6.84 (brs, 1H), 6.25 (d, 1H, J = 7.60 Hz), 5.01 – 4.91 (m, 1H), 3.73 (dd, 1H), 3.65 (dd, 1H), 3.45 – 3.25 (m, 8H), 2.56 (s, 3H); LCMS (M+H)⁺ m/z 479, 481.

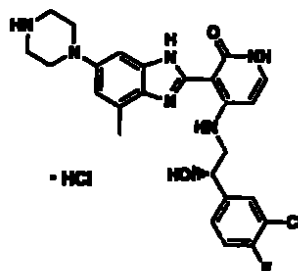
15 **Example 518**



(±)-4-[2-(3-Chloro-4-methylsulfanyl-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃OD) δ 7.47 (brs, 1H), 7.38 – 7.29 (m, 2H), 7.19 (d, 1H, J = 8.3 Hz), 7.03 (brs, 1H), 6.98 (brs, 1H), 6.26 (d, 1H, J = 7.7 Hz), 4.90 – 4.81 (m, 1H), 3.65 – 3.35 (m, 10H), 2.56 (s, 3H), 2.42 (s, 3H); LCMS (M+H)⁺ m/z 525, 527.

94

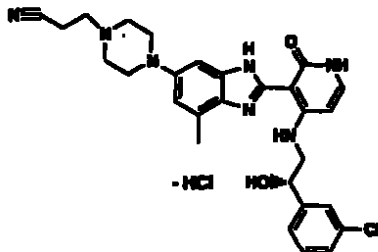
Example 519



- 5 (S)-4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (500 MHz, CD_3OD) δ 7.61 (dd, 1H, $J = 2.1, 7.2$ Hz), 7.40 (ddd, 1H), 7.28 (d, 1H, $J = 7.5$ Hz), 7.17 (dd, 1H, $J = 8.9, 8.8$ Hz), 7.02 (brs, 1H), 6.87 (brs, 1H), 6.25 (d, 1H, $J = 7.6$ Hz), 4.99 – 4.90 (m, 1H), 3.73 – 3.60 (m, 2H), 3.45 – 3.30 (m, 8H), 2.54 (s, 3H); LCMS
10 $(\text{M}+\text{H})^+$ m/z 497, 499.

The following examples (520-522) were prepared according to Scheme VII and III and illustrate the alkylation of a piperazine derivative

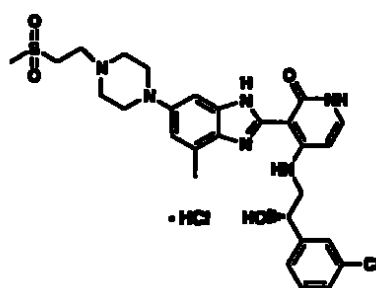
- 15 **Example 520 (General procedure for examples 520-522)**



- 20 (S)-3-[4-(2-(4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl)-piperazin-1-yl]-propionitrile: To a stirred solution of 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (17 mg, 0.021 mmol) in anhydrous methanol (1 mL) was added Hunigs base (36 μL). The resulting solution was cooled to 0 $^\circ\text{C}$ and acrylonitrile (5 μL) was added in portions until the reaction

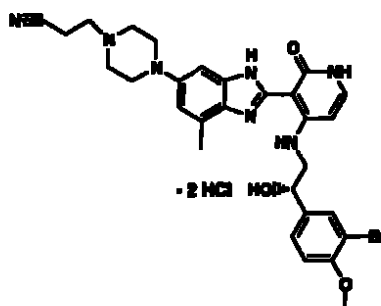
was complete as judged by LCMS. The reaction was warmed to room temperature and the solvent evaporated *in vacuo*. The resulting residue was purified on reverse phase preparative HPLC using a methanol / water / 0.1% trifluoroacetic acid gradient. The fractions were evaporated to give the title compound as a trifluoroacetic acid salt (12.1 mg): ¹H NMR (500 MHz, CD₃OD) δ 7.49 (brs, 1H), 7.39 – 7.23 (m, 4H), 7.15 (brs, 1H), 7.06 (brs, 1H), 6.25 (d, 1H, J = 7.7 Hz), 4.97 – 4.88 (m, 1H), 3.70 – 3.40 (m, 12 H), 3.06 (t, 2H, J = 7.0 Hz), 2.59 (s, 3H); LCMS (M+H)⁺ m/z 532,534. The trifluoroacetic acid salt of the pure title compound was dissolved in methanol and applied to a Varian Mega Bond-Elute SCX cartridge. Elution with methanol followed by 2.0 M NH₃ / MeOH gave the free base. This material was suspended in MeOH and 1.00 N aqueous HCl (2 equiv.) was added. The resulting solution was filtered through a 45 μm filter and evaporated to give the bis HCl salt of the title compound: ¹H NMR (300 MHz, CD₃OD) δ 7.50 – 7.25 (m, 5H), 7.16 (brs, 1H), 7.13 (brs, 1H), 6.27 (d, 1H, J = 7.7 Hz), 4.95 – 4.87 (m, 1H), 3.70 – 3.40 (m, 12H), 3.13 (t, 2H, J = 7.0 Hz), 2.62 (s, 3H); LCMS (M+H)⁺ m/z 532,534.

Example 521



(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃OD) δ 7.53 (brs, 1H), 7.41 – 7.20 (m, 4H), 7.13 (brs, 1H), 6.92 (brs, 1H), 6.24 (d, 1H, J = 7.6 Hz), 5.00 – 4.92 (m, 1H), 3.80 – 3.25 (m, 14H), 3.13 (s, 3H), 2.57 (s, 3H); LCMS (M+H)⁺ m/z 585, 587.

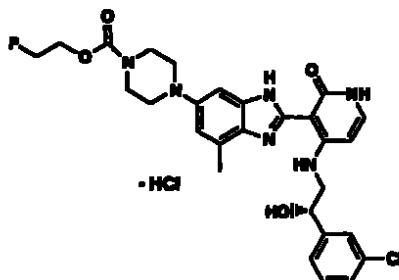
Example 522



- 5 (S)-3-[4-(2-(4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl)-piperazin-1-yl]-propionitrile: ^1H NMR (500 MHz, CD_3OD) δ 7.59 (brs, 1H), 7.41 (d, 1H, $J = 7.5$ Hz), 7.34 (dd, 1H, $J = 2.0, 8.5$ Hz), 7.17 (brs, 1H), 7.12 (brs, 1H), 7.00 (d, 1H, $J = 8.5$ Hz), 6.25 (d, 1H, $J = 7.5$ Hz), 4.85 – 4.76 (m, 1H), 3.85 (s, 3H), 3.80 – 3.30 (m, 12H),
 10 3.16 (t, 2H, $J = 7.0$ Hz), 2.55 (s, 3H); LCMS $(\text{M}+\text{H})^+$ m/z 606, 608.

The following examples (523-528) were prepared according to Scheme VII and III and illustrate the carbamoylation of a piperazine derivative

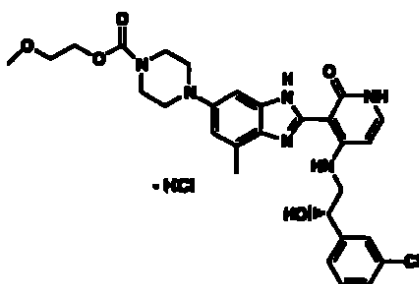
- 15 Example 523 (General procedure for examples 523-528)



- 20 (S)-4-(2-(4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carboxylic acid 2-fluoro-ethyl ester: To a stirred solution of 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (~ 2 TFA salt, 80 mg, ~0.1 mmol) in methanol (2 mL) at 0 °C was added N,N-

diisopropylethylamine (170 μ L) and 2-fluoroethyl chloroformate (37 mg). The cooling bath was removed and the solution was stirred at room temperature for 30 minutes, after which LC/MS analysis showed the reaction to be complete. The reaction mixture was then purified on reverse phase preparative HPLC using a methanol / water / 0.1% trifluoroacetic acid gradient. The fractions were evaporated to give the title compound as a trifluoroacetic acid salt, which was dissolved in methanol and applied to a Varian Mega Bond-Elute SCX cartridge. Elution with methanol followed by 2.0 M NH₃ / MeOH gave the free base (46.2 mg). This material was suspended in MeOH and 1.00 N aqueous HCl (1 equiv.) was added. The resulting solution was filtered through a 45 μ m filter and evaporated to give the mono HCl salt of the title compound (46 mg): ¹H NMR (500 MHz, CD₃OD) δ 7.50 (brs, 1H), 7.45 – 7.20 (m, 6H), 6.26 (d, 1H, J = 7.7 Hz), 4.98 – 4.91 (m, 1H), 4.64 (dm, 2H, J = 47.9 Hz), 4.39 (dm, 2H, J = 29 Hz), 3.95 – 3.50 (m, 10H), 2.63 (s, 3H); LCMS (M+H)⁺ m/z 569, 571.

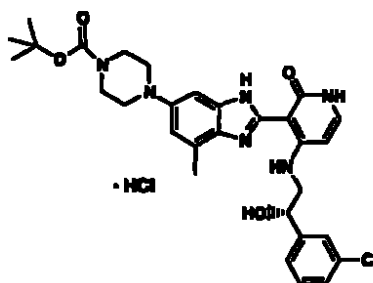
Example 524



(S)-4-(2-(4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carboxylic acid 2-methoxy-ethyl ester: ¹H NMR (500 MHz, CD₃OD) δ 7.53 – 7.22 (m, 7H), 6.26 (d, 1H, J = 7.6 Hz), 4.96 (dd, 1H, J = 7.0, 4.6 Hz), 4.31 – 4.27 (m, 2H), 4.05 – 3.55 (m, 12H), 3.39 (s, 3H), 2.64 (s, 3H); LCMS (M+H)⁺ m/z 581, 583.

96

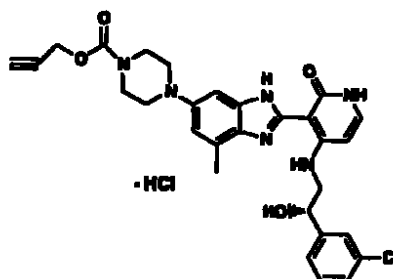
Example 525



- 5 (S)-4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzolimidazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester: ^1H NMR (500 MHz, CD_3OD) δ 7.51 (brs, 1H), 7.40 – 7.22 (m, 6H), 6.26 (d, 1H, $J = 7.7$ Hz), 4.96 – 4.90 (m, 1H), 3.90 – 3.30 (m, 10H), 2.64 (s, 3H), 1.51 (s, 9H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 579, 581.

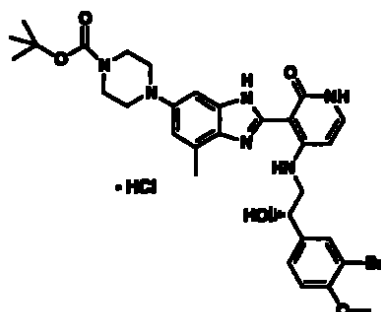
10

Example 526



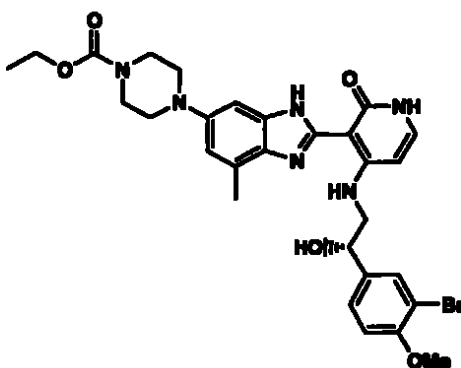
- 15 (S)-4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzolimidazol-5-yl)-piperazine-1-carboxylic acid prop-2-ynyl ester: ^1H NMR (500 MHz, CD_3OD) δ 7.50 (brs, 1H), 7.43 – 7.20 (m, 5H), 7.19 (brs, 1H), 6.25 (d, 1H, $J = 7.6$ Hz), 4.98 – 4.90 (m, 1H), 4.78 (d, 2H, $J = 2.5$ Hz), 3.95 – 3.30 (m, 10H), 2.97 (t, 1H, $J = 2.5$ Hz), 2.62 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z
- 20 561, 563.

Example 527



(S)-4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester: ^1H NMR (300 MHz, CD_3OD) δ 7.65 (brs, 1H), 7.48 – 7.28 (m, 3H), 7.25 (brs, 1H), 6.97 (d, 1H, $J = 8.5$ Hz), 6.25 (d, 1H, $J = 7.7$ Hz), 4.94 – 4.86 (m, 1H), 3.90 – 3.45 (m, 10H), 3.82 (s, 3H), 2.61 (s, 3H), 1.52 (s, 9H); LCMS $(\text{M}+\text{H})^+$ m/z 653, 655.

10 Example 528



(S)-4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carboxylic acid ethyl ester: ^1H NMR (400 MHz, CD_3OD) δ 7.80 (1H, s), 7.63 (1H, narrow d, $J = 1.8$ Hz), 7.52 (1H, s), 7.42 (1H, d, $J = 7.5$ Hz), 7.37 (1H, dd, $J = 1.8, 8.4$ Hz), 7.00 (1H, d, $J = 8.4$ Hz), 6.31 (1H, d, $J = 7.5$ Hz), 4.89 (1H, m), 4.22 (2H, q, $J = 7.1$ Hz), 3.98 (4H, br s), 3.84 (3H, s), 3.70 – 3.72 (4H, m), 3.59 – 3.60 (2H, m), 2.67 (3H, s), 1.31 (3H, t, $J = 7.1$ Hz).

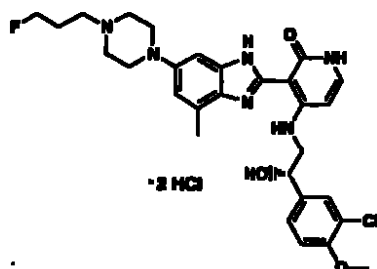
20 LCMS $(\text{M}+\text{H})^+$ m/z 625 ($t = 1.45$ min.).

97

The following examples (529-540) were prepared according to Scheme VII and III and illustrate an alternative method of alkylation of a piperazine derivative

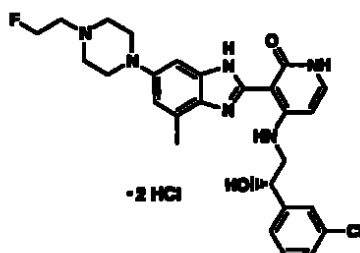
Example 529 (General procedure for examples 529-540)

5



(S)-4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoropropyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one: To a stirred solution of 4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one (100 mg, 0.162 mmol) in 1,4-dioxane (4.0 mL), ethanol (0.8 mL), methanol (0.8 mL) was added N,N-diisopropylethylamine (0.30 mL) and 1-bromo-3-fluoropropane (85 μ L). The reaction was heated at 80 °C for 12 h. The reaction mixture was then purified on reverse phase preparative HPLC using a methanol / water / 0.1% trifluoroacetic acid gradient. The fractions were evaporated to give the title compound as a trifluoroacetic acid salt, which was dissolved in methanol and applied to a Varian Mega Bond-Elute SCX cartridge. Elution with methanol followed by 2.0 M NH₃ / MeOH gave the free base (39.3 mg). This material was suspended in MeOH and 1.00 N aqueous HCl (2 equiv.) was added. The resulting solution was filtered through a 45 μ m filter and evaporated to give the bis HCl salt of the title compound (43.5 mg): ¹H NMR (400 MHz, CD₃OD) δ 7.43 – 7.37 (m, 2H), 7.28 (dd, 1H, J = 2.0, 8.6 Hz), 7.16 (brs, 1H), 7.08 (d, 1H, J = 1.7 Hz), 7.01 (d, 1H, J = 8.5 Hz), 6.24 (d, 1H, J = 7.7 Hz), 4.84 – 4.78 (m, 1H), 4.60 (dt, 2H, J = 5.7, 47.1 Hz), 3.95 – 3.88 (m, 2H), 3.83 (s, 3H), 3.78 – 3.71 (m, 2H), 3.53 – 3.14 (m, 8H), 2.59 (s, 3H), 2.31 – 2.16 (m, 2H); LCMS (M+H)⁺ m/z 569, 571.

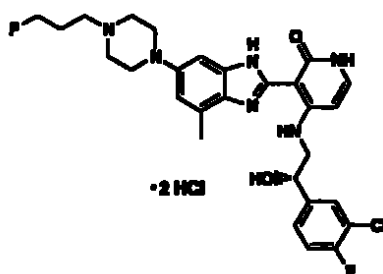
Example 530



- 5 (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoro-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ^1H NMR (400 MHz, CD_3OD) δ 7.45 – 7.20 (m, 5H), 7.16 (brs, 1H), 7.09 (brs, 1H), 6.25 (d, 1H, $J = 7.6$ Hz), 5.00 – 4.92 (m, 1H), 4.92 – 4.78 (m, 2H), 3.98 – 3.15 (m, 12H), 2.60 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 525, 527.

10

Example 531

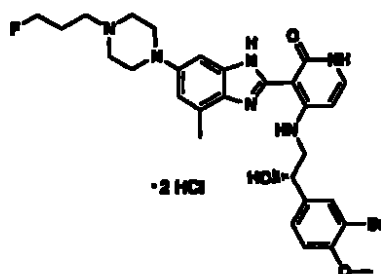


- 15 (S)-4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ^1H NMR (400 MHz, CD_3OD) δ 7.52 (dd, 1H, $J = 2.1, 7.2$ Hz), 7.40 (d, 1H, $J = 7.6$ Hz), 7.35 – 7.12 (m, 3H), 7.08 (d, 1H, $J = 1.7$ Hz), 6.25 (d, 1H, $J = 7.7$ Hz), 4.90 – 4.82 (m, 1H), 4.60 (dt, 2H, $J = 5.4, 47.1$ Hz), 3.96 – 3.10 (m, 12H), 2.60 (s, 3H), 2.28 – 2.13 (m, 2H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 557, 559.

20

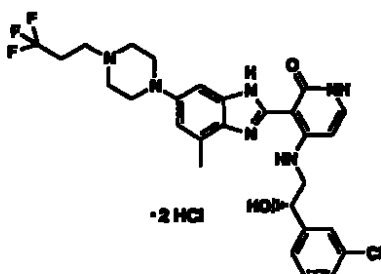
98

Example 532



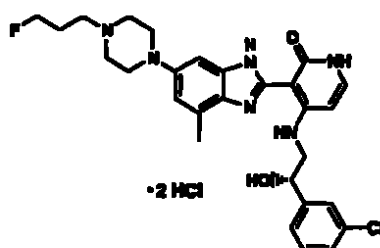
- 5 (S)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ^1H NMR (400 MHz, CD_3OD) δ 7.58 (d, 1H, $J = 2.0$ Hz), 7.43 (d, 1H, $J = 7.6$ Hz), 7.34 (dd, 1H, $J = 2.0, 8.5$ Hz), 7.19 (brs, 1H), 7.11 (brs, 1H), 7.00 (d, 1H, $J = 8.5$ Hz), 6.26 (d, 1H, $J = 7.7$ Hz), 5.90 – 4.82 (m, 1H), 4.61 (dt, 2H, $J = 5.4, 47.1$ Hz), 3.95 – 3.12 (m, 12H), 3.85 (s, 3H), 2.62 (s, 3H), 2.30 – 2.14 (m, 2H); LCMS $(\text{M}+\text{H})^+$ m/z 613, 615.
- 10

Example 533



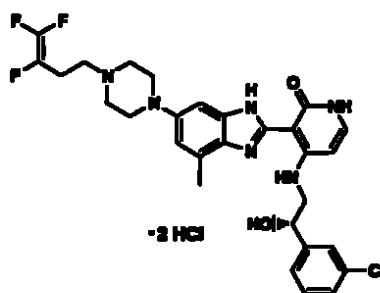
15

- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-[4-(3,3,3-trifluoro-propyl)-piperazin-1-yl]-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ^1H NMR (300 MHz, CD_3OD) δ 7.50 – 7.10 (m, 7H), 6.26 (d, 1H, $J = 7.5$ Hz), 4.96 – 4.88 (m, 1H), 4.00 – 3.15 (m, 12H), 3.00 – 2.82 (m, 2H), 2.61 (s, 3H); LCMS $(\text{M}+\text{H})^+$ m/z 575, 577.
- 20

Example 534

- 5 **(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzolimidazol-2-yl}-1H-pyridin-2-one:** ^1H NMR (300 MHz, CD_3OD) δ 7.46 – 7.25 (m, 5H), 7.19 (brs, 1H), 7.11 (brs, 1H), 6.27 (d, 1H, $J = 7.7$ Hz), 4.95 – 4.86 (m, 1H), 4.62 (dt, 2H, $J = 5.4, 47.1$ Hz), 3.98 – 3.15 (m, 12H), 2.62 (s, 3H), 2.35 – 2.12 (m, 2H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 539, 541.

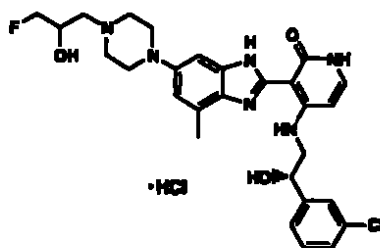
10

Example 535

- 15 **(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(3,4,4-trifluoro-but-3-enyl)-piperazin-1-yl]-1H-benzolimidazol-2-yl}-1H-pyridin-2-one:** LCMS ($\text{M}+\text{H}$) $^+$ m/z 587, 589.

Example 536

20

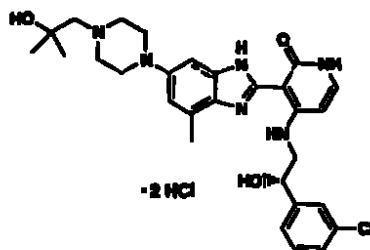


99

4-[2-(3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-2-hydroxy-propyl)-piperazin-1-yl]-4-methyl-1*H*-benzimidazol-2-yl}-1*H*-pyridin-2-one:
LCMS (M+H)⁺ m/z 555, 557.

5

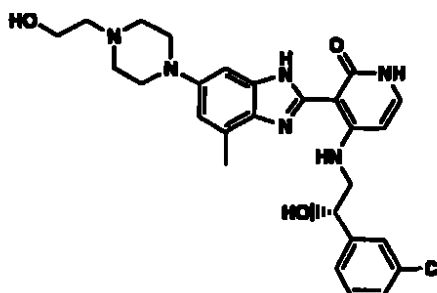
Example 537



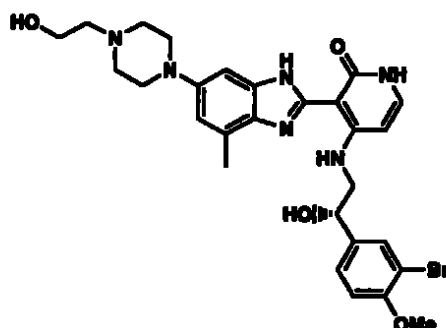
- 10 (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-2-methyl-propyl)-piperazin-1-yl]-4-methyl-1*H*-benzimidazol-2-yl}-1*H*-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.44 – 7.22 (m, 5H), 7.15 (brs, 1H), 7.08 (brs, 1H), 6.25 (d, 1H, J = 7.6 Hz), 4.88 – 4.80 (m, 1H), 3.86 – 3.81 (m, 4H), 3.55 – 3.32 (m, 6H), 3.28 (s, 2H), 2.60 (s, 3H), 1.38 (s, 6H); LCMS (M+H)⁺ m/z 551, 553.

15

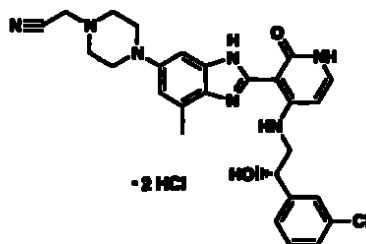
Example 538



- 20 (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1*H*-benzimidazol-2-yl}-1*H*-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.50 (1H, s), 7.25 – 7.35 (4H, m), 7.04 (1H, s), 6.97 (1H, s), 6.22 (1H, d, J = 6.8 Hz), 4.93 – 4.95 (1H, m), 3.21 – 3.96 (14H, m), 2.57 (3H, s). LCMS (M+H)⁺ m/z 523 (t = 1.11 min.).

Example 539

- 5 **(S)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:** ^1H NMR (400 MHz, CD_3OD) δ 7.60 (1H, narrow d, $J = 2.0$ Hz), 7.40 (1H, d, $J = 7.6$ Hz), 7.35 (1H, dd, $J = 2.0, 8.4$ Hz), 7.13 (1H, s), 7.09 (1H, s), 6.99 (1H, d, $J = 8.4$ Hz), 6.25 (1H, d, $J = 7.6$ Hz), 4.82 – 4.87 (1H, m), 3.76 – 3.97 (6H, m), 3.84 (3H, s),
 10 3.24 – 3.52 (8H, m), 2.60 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 597 ($t = 1.09$ min.).

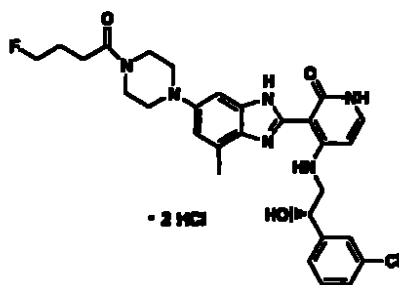
Example 540

15

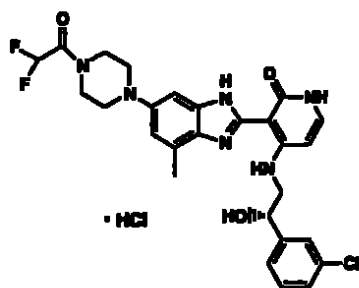
- (S)-[4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-piperazin-1-yl]-acetonitrile:** ^1H NMR (400 MHz, CD_3OD) δ 7.50 – 7.25 (m, 7H), 6.28 (d, 1H, $J = 8.0$ Hz), 4.95 – 4.88 (m, 1H), 4.32 (s, 2H), 3.75 – 3.62 (m, 4H), 3.60 – 3.35 (m, 6H), 2.63 (s, 3H); LCMS
 20 $(\text{M}+\text{H})^+$ m/z 518, 520.

The following examples (541-553) were prepared according to Scheme VII and III and illustrate the acylation of a piperazine derivative

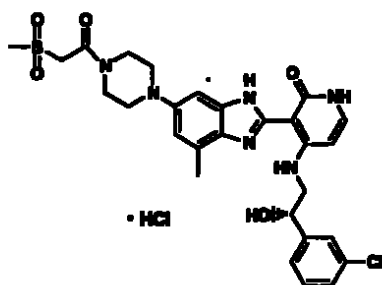
100

Example 541 (General procedure for examples 541-553)

- 5 **(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(4-fluoro-butyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:** To a stirred solution of 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (70 mg, 0.136 mmol) in anhydrous N,N-dimethylformamide (750 μ l) was added 1-(3-dimethylaminopropyl)-3-
- 10 ethylcarbodiimide hydrochloride (112 mg, 0.584 mmol), 1-hydroxybenzotriazole hydrate (59 mg, 0.438 mmol), N-methylmorpholine (0.048 mL, 0.438 mmol) and 4-fluorobutyric acid (31 mg, 0.291 mmol; see O'Hagan, D., *J. Fluorine Chem.*, 43, (1989), 371-377) and the mixture heated to 80 $^{\circ}$ C for 3 h. The reaction mixture was then purified on reverse phase preparative HPLC using a methanol / water / 0.1%
- 15 trifluoroacetic acid gradient. The fractions were evaporated to give the title compound as a trifluoroacetic acid salt, which was dissolved in methanol and applied to a Varian Mega Bond-Elute SCX cartridge. Elution with methanol followed by 2.0 M NH₃ / MeOH gave the free base (35.9 mg). This material was suspended in MeOH and 1.00 N aqueous HCl (2 equiv.) was added. The resulting solution was filtered
- 20 through a 45 μ m filter and evaporated to give the bis HCl salt of the title compound (37.6 mg): ¹H NMR (400 MHz, CD₃OD) δ . 7.61 (brs, 1H), 7.47 (brs, 1H), 7.44 – 7.20 (m, 5H), 6.27 (d, 1H, J = 7.6 Hz), 4.92 (dd, 1H, J = 4.4, 7.3 Hz), 4.50 (dt, 2H, J = 5.9, 47.3 Hz), 4.05 – 3.40 (m, 10H), 2.64 (s, 3H), 2.63 (t, 2H, J = 7.6 Hz), 2.09 – 1.95 (m, 2H); LCMS (M+H)⁺ m/z 567, 569.

Example 542

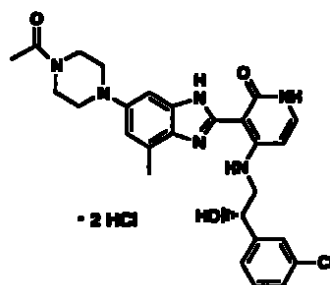
- 5 **(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2,2-difluoro-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one:** LCMS $(M+H)^+$ m/z 557, 559.

Example 543

10

- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfonyl-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one:** LCMS $(M+H)^+$ m/z 599, 601.

15

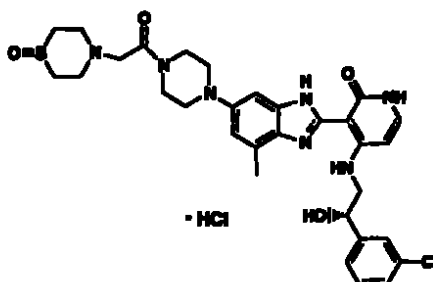
Example 544

- 20 **(S)-3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzoimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one:** ^1H NMR (500 MHz,



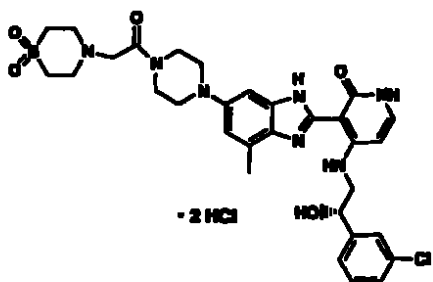
CD₃OD) δ 7.57 (brs, 1H), 7.49 (brs, 1H), 7.40 – 7.20 (m, 5H), 6.29 (d, 1H, J = 7.6 Hz), 4.98 – 4.90 (m, 1H), 4.02 – 3.91 (m, 4H), 3.70 – 3.50 (m, 6H), 2.66 (s, 3H), 2.21 (s, 3H); LCMS (M+H)⁺ m/z 521, 523.

5 Example 545



(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-[4-[2-(1-oxo-1,4-thiomorpholin-4-yl)-acetyl]-piperazin-1-yl]-1H-benzimidazol-2-yl)-1H-pyridin-2-one: LCMS (M+H)⁺ m/z 638, 640.

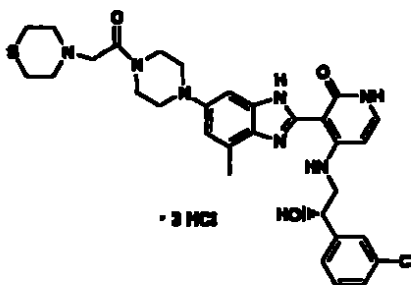
Example 546



15

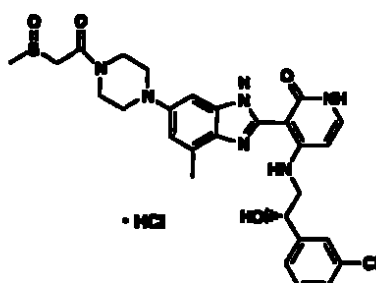
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-[4-[2-(1,1-dioxo-1,4-thiomorpholin-4-yl)-acetyl]-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: LCMS (M+H)⁺ m/z 654, 656.

20 Example 547



(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(2-thiomorpholin-4-yl-acetyl)-piperazin-1-yl]-1H-benzimidazol-2-yl}-1H-pyridin-2-one: LCMS (M+H)⁺ m/z 622, 624.

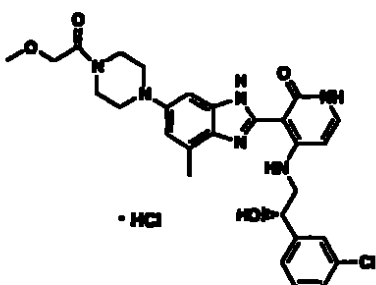
Example 548



10

4-[2-(3-Chloro-phenyl)-2(S)-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfinyl-acetyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: LCMS (M+H)⁺ m/z 583, 585.

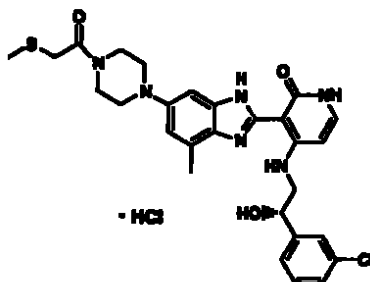
Example 549



(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methoxy-acetyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃OD) δ 7.49 (brs, 1H), 7.40 – 7.18 (m, 6H), 6.26 (d, 1H, J = 7.7 Hz),

20

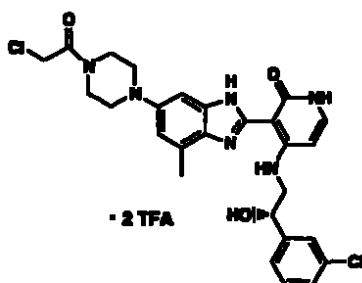
4.98 – 4.90 (m, 1H), 4.25 (s, 2H), 3.95 – 3.46 (m, 10H), 3.44 (s, 3H), 2.63 (s, 3H);
LCMS (M+H)⁺ m/z 551, 553.

Example 550

5

(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(2-methylsulfanylmethyl)-acetyl]-piperazin-1-yl]-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃OD) δ 7.49 (brs, 1H), 7.45 – 7.20 (m, 6H), 6.26 (d, 1H, J = 7.60 Hz), 4.98 – 4.90 (m, 1H), 3.97 – 3.40 (m, 12H), 2.63 (s, 3H), 2.20 (s, 3H);
LCMS (M+H)⁺ m/z 567, 569.

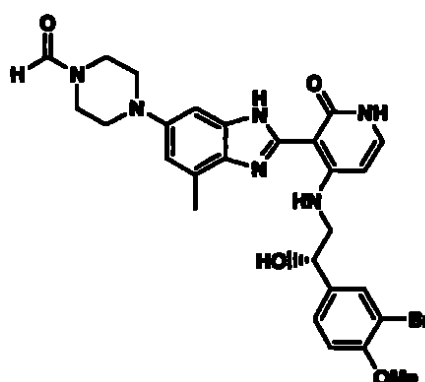
10

Example 551

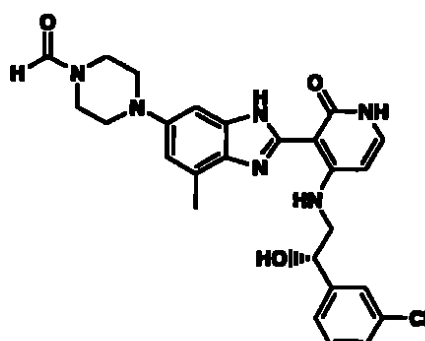
15

(S)-3-{6-[4-(2-Chloro-acetyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃OD) δ 7.49 (brs, 1H), 7.38 – 7.20 (m, 5H), 7.15 (brs, 1H), 6.25 (d, 1H, J = 7.6 Hz), 4.98 – 4.90 (m, 1H), 4.35 (s, 2H), 3.90 – 3.80 (m, 4H), 3.66 – 3.30 (m, 6H), 2.61 (s, 3H); LCMS (M+H)⁺ m/z 555, 557.

20

Example 552

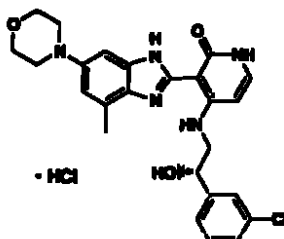
- 5 **(S)-4-(2-(4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carbaldehyde:** ^1H NMR (400 MHz, CD_3OD) δ 8.18 (1H, s), 7.65 (1H, s), 7.61 (1H, narrow d, $J = 2.0$ Hz), 7.46 (1H, s), 7.43 (1H, d, $J = 7.6$ Hz), 7.36 (1H, dd, $J = 2.0, 8.5$ Hz), 7.00 (1H, d, $J = 8.5$ Hz), 6.32 (1H, d, $J = 7.6$ Hz), 4.86 – 4.89 (1H, m), 3.91 –
- 10 3.96 (4H, m), 3.84 (3H, s), 3.57 – 3.67 (7H, m), 2.66 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 581 ($t = 1.24$ min.).

Example 553

- 15 **(S)-4-(2-(4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carbaldehyde:** ^1H NMR (400 MHz, CD_3OD) δ 8.12 (1H, s), 7.50 (1H, s), 7.24 – 7.38 (6H, m), 6.23 (1H, d, $J = 7.6$ Hz), 4.93 – 4.96 (1H, m), 3.54 – 3.79 (10H, m), 2.58 (3H, s). LCMS
- 20 $(\text{M}+\text{H})^+$ m/z 507 ($t = 1.29$ min.).

The following examples (Examples 554-575) were prepared according to Scheme VII and III

Example 554



5

(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: To a suspension of 4-Chloro-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one and the
10 corresponding iodo compound 4-Iodo-3-(4-methyl-6-morpholin-4-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one (4.43 g, ~ 11 mmol) in acetonitrile (100 ml) triethylamine (7.0 ml, 50 mmol) and 2-(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamine hydrochloride (2.55 g, 12.2 mmol) were added. The mixture was stirred at 85°C overnight. LCMS showed some starting material pyridone left. 2-(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamine hydrochloride (0.22 g, 1.06 mmol) was added and the
15 mixture stirred at 85°C another 24 hours. After evaporation of volatiles an aqueous solution of Cs₂CO₃ (200 ml, 10%) was added, the suspension sonicated for 5 minutes and stirred overnight. The product was filtered, washed with water and recrystallized from methanol - chloroform. The title compound was isolated as yellow crystals.
20 (3.951 g, 75%). LCMS (M+H)⁺ m/z 480 (t = 1.31 min.). HPLC t = 4.93 min, YMC-Pack ODS-A 3.0 x 50 mm; 0 - 100% gradient over 8 min; 2.5 mL/min flow rate. ¹H NMR of mono-HCl salt (500 MHz, DMSO-d₆) δ 13.3 (1H, broad s), 11.22 (1H, s), 10.9 (1H, broad s), 7.65 (1H, broad s), 7.60 (1H, s), 7.45 (d, J = 7.6 Hz), 7.38-7.30 (4H, m) 6.19 (1H, d, J = 7.5 Hz), 4.92 (1H, t, J = 5.3 Hz), 4.00 (6H, broad), 3.67 (1H, m), 3.52 (5H, m), 2.58 (3H, s).
25

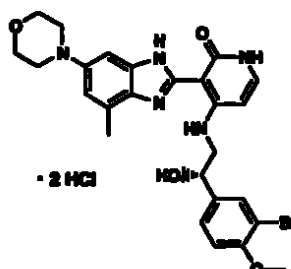
General procedure for preparation of mono- and bis- HCl salts:

A solution or suspension of free base in methanol is treated with 1.00 (or 2.00 resp.) equivalent of 1.00 N aqueous HCl. If significant amounts of compound remain

insoluble an equal volume of dichloroethane is added to improve solubility. The mixture is filtered and concentrated *in vacuo*. Small amounts were evaporate to dryness, large-scale preparations for *in vivo* studies were concentrated until most of the compound crystallized, then filtered.

5

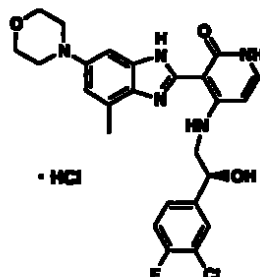
Example 555



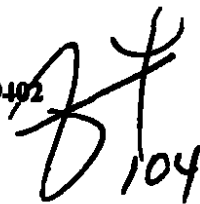
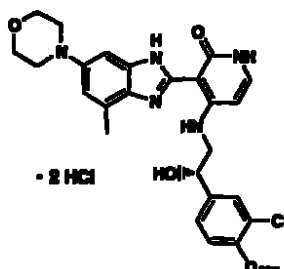
- 10 (S)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (300 MHz, CD_3OD) δ 7.68 – 7.60 (m, 2H), 7.43 – 7.28 (m, 3H), 6.98 (d, 1H, $J = 8.50$ Hz), 6.26 (d, 1H, $J = 7.7$ Hz), 4.97 – 4.89 (m, 1H), 4.18 – 4.04 (m, 4H), 3.82 (s, 3H), 3.73 – 3.55 (m, 6H), 2.63 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 554, 556.

15

Example 556



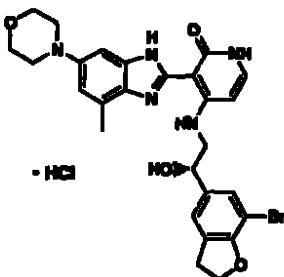
- 20 (S)-4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (300 MHz, CD_3OD) δ 7.65 – 7.50 (m, 2H), 7.43 – 7.20 (m, 3H), 7.18 (dd, 1H, $J = 8.9, 8.8$ Hz), 6.27 (d, 1H, $J = 7.6$ Hz), 5.00 – 4.91 (m, 1H), 4.15 – 4.02 (m, 4H), 3.75 – 3.60 (m, 6H), 2.64 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 498, 500.


Example 557

5

(S)-4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (400 MHz, CD_3OD) δ 7.67 (brs, 1H), 7.45 (brs, 1H), 7.40 – 7.28 (m, 3H), 7.00 (d, 1H, $J = 8.4$ Hz), 6.27 (d, 1H, $J = 7.6$ Hz), 4.95 – 4.84 (m, 1H), 4.15 – 4.05 (m, 4H), 3.82 (s, 3H), 3.75 – 3.55 (m, 6H), 2.64 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 510, 512.

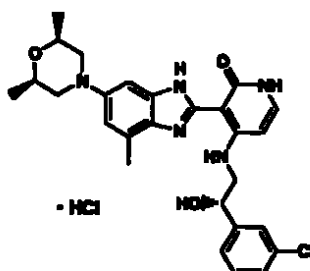
10

Example 558

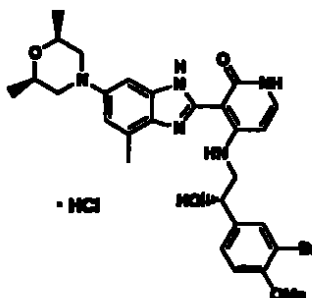
15

(S)-4-[2-(7-Bromo-2,3-dihydro-benzofuran-5-yl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one: ^1H NMR (400 MHz, CD_3OD) δ 7.54 (brs, 1H), 7.35 – 7.30 (m, 2H), 7.27 (brs, 1H), 7.22 (brs, 1H), 6.27 (d, 1H, $J = 7.6$ Hz), 4.95 – 4.87 (m, 1H), 4.60 – 4.50 (m, 2H), 4.10 – 4.00 (m, 4H), 3.75 – 3.60 (m, 6H), 3.25 – 3.13 (m, 2H), 2.62 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 566, 568.

20

Example 559

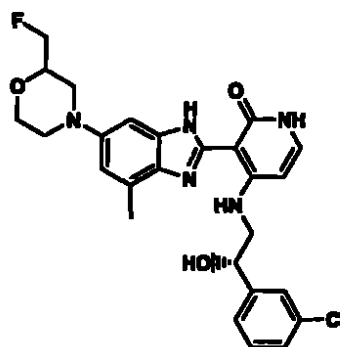
- 5 **4-[2-(3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-[2(*S*),6(*R*)-dimethyl-morpholine-4-yl]-1H-benzimidazol-2-yl]-1H-pyridine-2-one.** ¹H NMR (400 MHz, CD₃OD) δ 7.23-7.57 (7H, - m), 6.22 (1H, d, *J* = 7.6 Hz), 4.97 (1H, m), 4.06 (2H, m), 3.62-3.68 (4H, m), 3.20-3.34 (2H, m), 2.63 (3H, s), 1.30 (6H, d, *J* = 6.28 Hz), LCMS (M+H)⁺ *m/z* 508 (*t* = 2.12 min.)

10 **Example 560**

- 15 **4-[2-(3-Bromo-4-methoxy-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-[2(*S*),6(*R*)-dimethyl-morpholine-4-yl]-1H-benzimidazol-2-yl]-1H-pyridine-2-one.** ¹H NMR (400 MHz, CD₃OD) δ 7.73 (1H, s), 7.63 (1H, s), 7.42 (1H, s), 7.34 (2H, m), 6.96 (1H, d, *J* = 8.48 Hz), 6.21 (1H, d, *J* = 7.48 Hz), 4.87 (1H, m), 4.23 (2H, m), 3.57-3.67(4H, m), 3.34 (3H, s) 3.30-3.32(2H, m), 2.60 (1H, s), 1.30 (6H, d, *J* = 6.2 Hz) LCMS (M+H)⁺ *m/z* 582 (*t* = 2.03 min.)

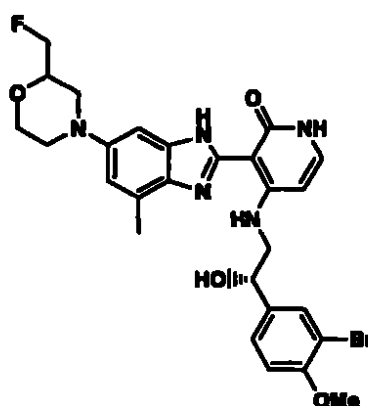
8/105

Example 561



4-[2-(3-Chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.47 (1H, s), 7.23 – 7.43 (6H, m), 6.22 (1H, d, J = 7.2 Hz), 4.87 – 4.94 (1H, m), 4.60 (1H, d, J = 3.4 Hz), 4.48 (1H, d, J = 3.4 Hz), 4.04 – 4.15 (3H, m), 3.28 – 3.62 (6H, m), 2.56 (3H, s). LCMS (M+H)⁺ m/z 512 (t = 1.35 min.).

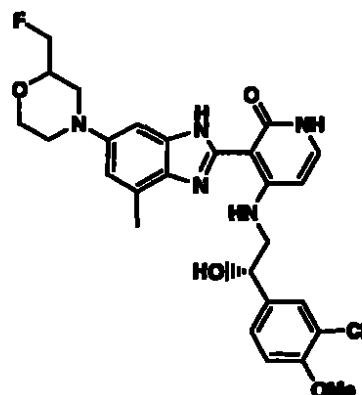
Example 562



4-[2-(3-Bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.60 (1H, narrow d, J = 2.0 Hz), 7.56 (1H, s), 7.39 (1H, br s), 7.34 (1H, dd, J = 2.0, 8.4 Hz), 6.97 (1H, d, J 8.4 Hz), 6.27 (1H, d, J =

6.4 Hz), 4.86 (1H, m), 4.61 (1H, m), 4.50 (1H, m), 4.77 – 4.19 (3H, m), 3.82 (3H, s), 3.38 – 3.74 (8H, m), 2.63 (3H, s). LCMS (M+H)⁺ m/z 586 (t = 1.31 min.).

Example 563

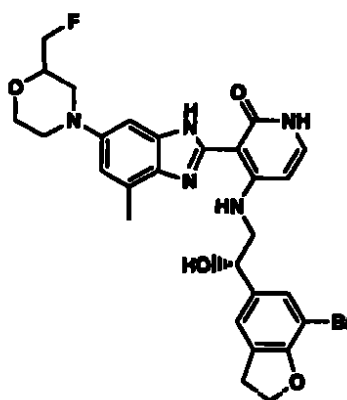


5

4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.45 (1H, s), 7.28 – 7.30 (3H, m), 7.10 (1H, s), 6.97 (1H, d, J = 8.0 Hz), 6.20 (1H, d, J = 6.4 Hz), 4.85 (1H, m), 4.58 (1H, br s), 4.46 (1H, br s), 3.93 – 4.10 (3H, m), 3.80 (3H, s), 3.59 (4H, m), 3.07 – 3.29 (2H, m), 2.55 (3H, s). LCMS (M+H)⁺ m/z 542 (t = 1.28 min.).

15

Example 564

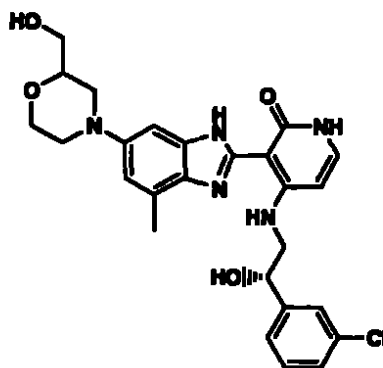


26
106

4-[2-(7-Bromo-2,3-dihydro-benzofuran-5-yl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(7-bromo-2,3-dihydro-benzofuran-5-yl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-

- 5 benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.26 -7.40 (4H, m), 7.19 (1H, s), 6.24 (1H, d, *J* = 7.6 Hz), 4.81 - 4.82 (1H, m), 4.49 - 4.61 (4H, m), 3.18 - 4.18 (11H, m), 2.59 (3H, s). LCMS (M+H)⁺ *m/z* 598 (*t* = 1.32 min.).

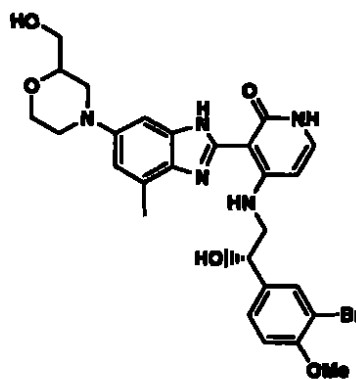
Example 565



10

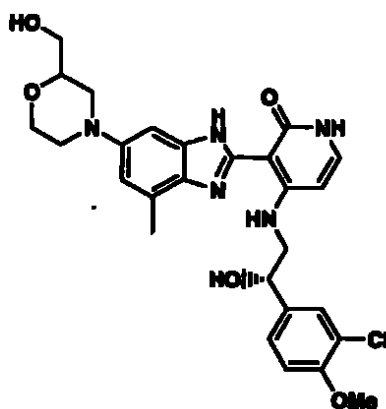
- 4-[2-(3-Chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro -phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.49 (1H, s), 7.23 - 7.37 (6H, m), 7.10 (1H, s), 6.24 (1H, d, *J* = 7.6 Hz), 4.95 - 4.96 (1H, m), 4.19 (1H, m), 3.94 - 4.80 (2H, m), 3.59 - 3.71 (8H, m), 2.63 (3H, s). LCMS (M+H)⁺ *m/z* 510 (*t* = 1.21 min.).

20 Example 566

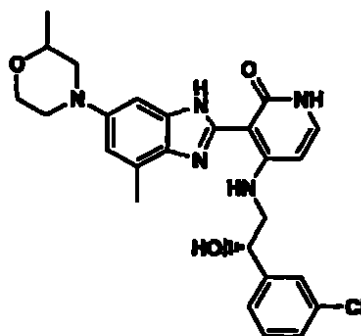


4-[2-(3-Bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.62 (1H, narrow d, *J* = 2.0 Hz), 7.54 (1H, s), 7.29 – 7.36 (3H, m), 6.95 (1H, d, *J* = 8.4 Hz), 6.23 (1H, d, *J* = 7.6 Hz), 4.88 – 4.89 (1H, m), 3.56 – 4.19 (11H, m), 3.80 (3H, s), 2.60 (3H, s). LCMS (M+H)⁺ *m/z* 584 (*t* = 1.16 min.).

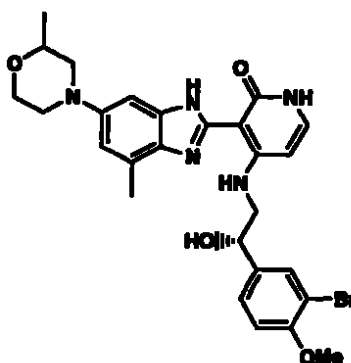
10 Example 567



4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.68 (1H, s), 7.54 (1H, s), 7.45 (1H, s), 7.39 (1H, s), 7.30 – 7.32 (2H, m), 6.98 (1H, d, *J* = 8.4 Hz), 6.22 (1H, d, *J* = 7.6 Hz), 4.89 (1H, m), 4.11 – 4.19 (3H, m), 3.80 (3H, s), 3.49 – 3.72 (8H, m), 2.60 (3H, s). LCMS (M+H)⁺ *m/z* 540 (*t* = 1.09 min.).

Example 568

4-[2-(3-Chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.75 (1H, s), 7.48 (1H, s), 7.42 (1H, s), 7.23 – 7.37 (4H, m), 6.24 (1H, d, *J* = 7.2 Hz), 4.94 – 4.97 (1H, m), 4.11 – 4.16 (3H, m), 3.61 – 3.68 (5H, m), 3.38 (1H, m), 2.64 (3H, s), 1.29 (3H, d, *J* = 6.4 Hz). LCMS (M+H)⁺ *m/z* 494 (*t* = 1.32 min.).

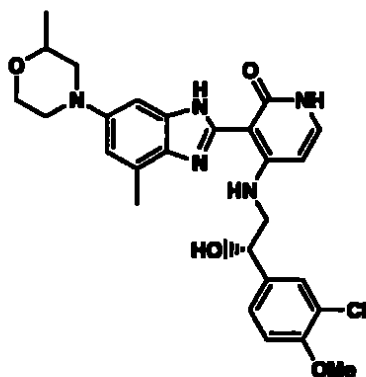
Example 569

4-[2-(3-Bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.63 (1H, s), 7.62 (1H, s), 7.30 – 7.61 (3H, m), 6.95 (1H, d, *J* = 8.4 Hz), 6.22 (1H, d, *J* = 7.6 Hz), 4.88 – 4.90 (1H, m), 4.08 – 4.18 (3H, m), 3.80 (3H,

s), 3.61 – 3.67 (5H, m), 3.32 – 3.34 (1H, m), 2.60 (3H, s), 1.28 (3H, d, $J = 6.0$ Hz).

LCMS ($M+H$)⁺ m/z 568 ($t = 1.31$ min.).

Example 570

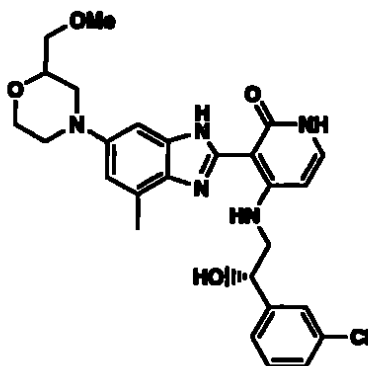


5

4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methyl-
 10 **morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:** ¹H NMR (400 MHz, CD₃OD) δ 7.48 (1H, narrow d, $J = 2.0$ Hz), 7.40 (1H, br s), 7.31 (1H, narrow d, $J = 2.0$ Hz), 7.29 (1H, narrow d, $J = 2.0$ Hz), 6.97 (1H, d, $J = 8.4$ Hz), 6.22 (1H, d, $J = 7.6$ Hz), 4.87 – 4.90 (1H, m), 4.11 (1H, m), 3.95 – 4.01 (2H, m), 3.80 (3H, s), 3.47 (4H, m), 3.32 (1H, m), 3.25 (1H, m), 2.57 (3H, s), 1.27 (3H, d, $J = 6.4$ Hz).

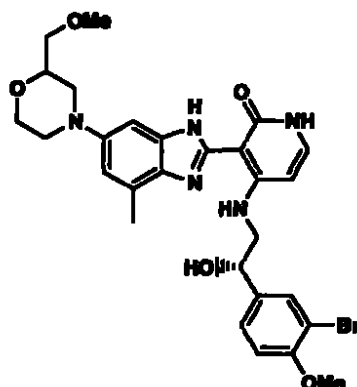
15 LCMS ($M+H$)⁺ m/z 525 ($t = 1.27$ min.).

Example 571

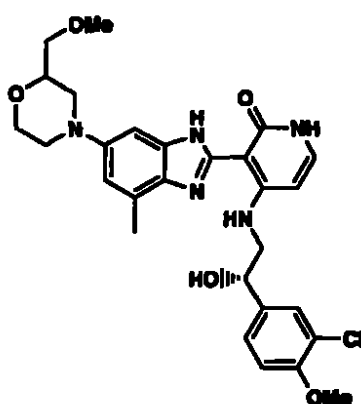


20 **4-[2-(3-Chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-**

chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methoxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one; ¹H NMR (400 MHz, CD₃OD) δ 7.49 (1H, narrow d, *J* = 2.0 Hz), 7.23 – 7.36 (6H, m), 6.22 (1H, d, *J* = 7.2 Hz), 4.93 – 4.96 (1H, m), 4.08 – 4.21 (11H, m), 3.38 (3H, s), 2.60 (3H, s), 1.27 (3H, d, *J* = 6.4 Hz). LCMS (M+H)⁺ *m/z* 524 (*t* = 1.35 min.).

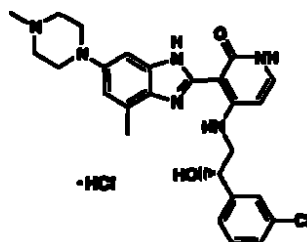
Example 572

4-[2-(3-Bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.63 (1H, narrow d, *J* = 2.0 Hz), 7.40 (1H, br s), 7.30 – 7.36 (3H, m), 7.19 (1H, br s), 6.95 (1H, d, *J* = 8.4 Hz), 6.23 (1H, d, *J* = 7.2 Hz), 4.87 – 4.89 (1H, m), 4.18 (1H, m), 3.97 – 4.03 (3H, m), 3.80 (3H, s), 3.54 – 3.66 (7H, m), 3.39 (3H, s), 2.59 (3H, s). LCMS (M+H)⁺ *m/z* 598 (*t* = 1.31 min.).

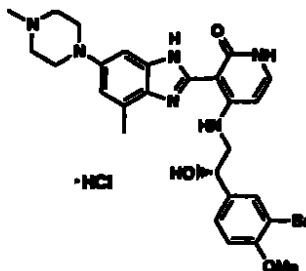
Example 573

4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.52 (1H, s), 7.46 (1H, narrow d, *J* = 1.6 Hz), 7.29–7.34 (3H, m), 6.99 (1H, d, *J* = 8.4 Hz), 6.24 (1H, d, *J* = 7.2 Hz), 4.89 (1H, m), 4.06–4.17 (3H, m), 3.81 (3H, s), 3.54–3.68 (8H, m), 3.38 (3H, s), 2.60 (3H, s). LCMS (M+H)⁺ *m/z* 554 (*t* = 1.28 min.).

10

Example 574

4-[2-(3-Chloro-phenyl)-2(S)-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridine-2-one. ¹H NMR (400 MHz, CD₃OD) δ 7.46 (1H, s), 7.24–7.36 (m, 4H), 7.04 (2H, s), 6.22 (1H, d, *J* = 7.64 Hz), 4.89 (1H, m), 3.30–3.82 (10H, m) 2.97 (3H, s), 2.57 (3H, s). LCMS (M+H)⁺ *m/z* 493 (*t* = 1.56 min.)

20 **Example 575**

4-[2-(3-Bromo-4-methoxy-phenyl)-2(S)-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridine-2-one. ¹H NMR

26
109

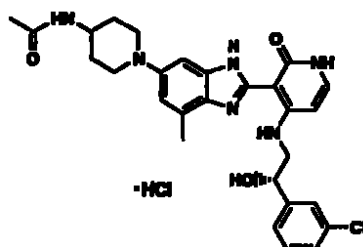
(400 MHz, CD₃OD) δ 7.61 (1H, d, J = 2.0 Hz), 7.32-7.37 (2H, m), 7.05 (2H, s), 6.97 (1H, d, J = 8.52 Hz), 6.24 (1H, d, J = 7.64 Hz), 4.82 (1H, m), 3.82 (3H, s) 3.30-3.64 (10H, m), 2.98 (3H, s), 2.56 (3H, s) LCMS (M+H)⁺ m/z 567 (t = 1.53 min.)

5

The following examples (576-581) were prepared according to Scheme VII and III and illustrate the acylation of a 4-amino-piperidine derivative

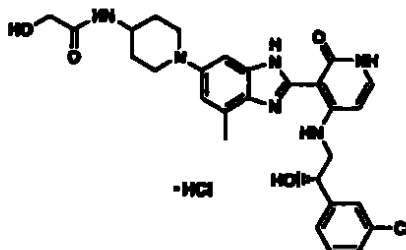
Example 576 (General procedure for Examples 576-581)

10



4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-[4-(acetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one: A solution of the 4-amino-piperidine compound (~ 50-100 μ mol) in 5 ml MeOH is cooled to 0°C. Then ~10 equivalent of Huenigs base and ~ 3 equivalent of acyl chloride are added. The vial is shaken once and allowed to stand at ambient temperature for 1 hour. Evaporation of volatiles and purification by prep. HPLC gives the 4-acyl-aminopiperidine compounds. ¹H NMR (500 MHz, CD₃OD) δ 8.06 (1H, s), 7.68 (1H, s), 7.49 (1H, s), 7.44 (1H, d, J = 7.6), 7.27 – 7.38 (4H, m), 6.33 (1H, d, J = 7.6 Hz), 4.96 (1H, dd, J = 4.1, 7.6 Hz), 4.17 (1H, m), 3.87 (4H, m), 3.65 (1H, dd, J = 4.2, 14 Hz), 3.58 (1H, dd, J = 7.8, 13.8 Hz), 2.72 (3H, s), 2.31 (2H, m), 2.19 (2H, m), 2.02 (3H, s). LCMS (M+H)⁺ m/z 535 (t = 1.03 min, YMC Xterra C18 S7 3.0 x 50 mm; 0 - 100% gradient over 1.5 min; 5 mL/min flow rate).

25

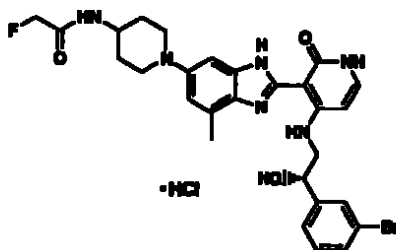
Example 577

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxyacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:

LCMS (M+H)⁺ m/z 551 (t = 1.27 min.). HPLC t = 5.01 min, Waters Xterra C18 S5 4.6 x 30 mm; 0 - 100% gradient over 12 min; 5 mL/min flow rate.

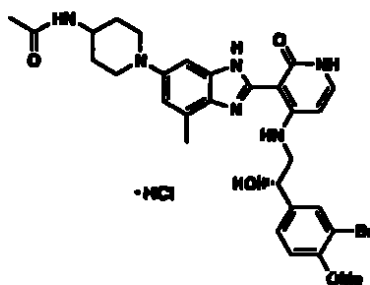
Example 578

10



4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:

LCMS (M+H)⁺ m/z 597 (t = 1.31 min.). HPLC t = 6.90 min, YMC-Pack ODS-A 3.0 x 50 mm, 0 - 100% gradient over 12 min; 2.5 mL/min flow rate.

Example 579

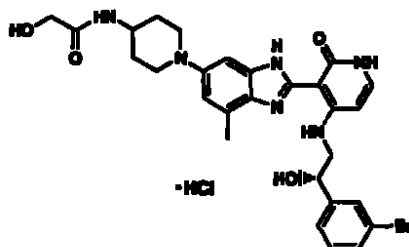
20

110

4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(acetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:

LCMS (M+H)⁺ m/z 609 (t = 1.27 min.). HPLC t = 5.00 min, Waters Xterra C18 S5 4.6 x 30 mm; 0 - 100% gradient over 12 min; 5 mL/min flow rate.

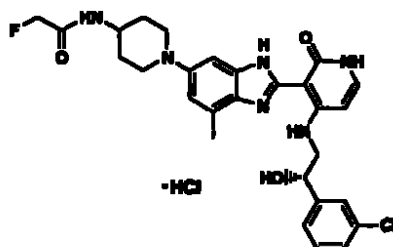
5

Example 580

4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxyacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:

10

LCMS (M+H)⁺ m/z 595 (t = 1.30 min.). HPLC t = 5.09 min, Waters Xterra C18 S5 4.6 x 30 mm; 0 - 100% gradient over 12 min; 5 mL/min flow rate.

Example 581

15

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:

LCMS (M+H)⁺ m/z 553 (t = 1.35 min.). HPLC t = 5.90 min, YMC-Pack ODS-A 3.0 x 50 mm; 0 - 100% gradient over 10 min; 2.5 mL/min flow rate.

20

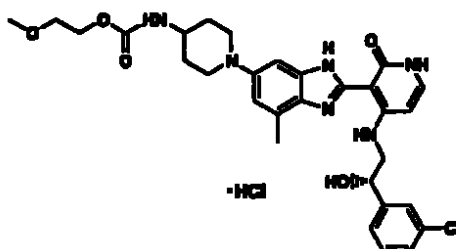
The following examples (582-584) were prepared according to Scheme VII and III and illustrate the carbamoylation of a 4-amino-piperidine derivative

General Procedure for Examples 582-584

25

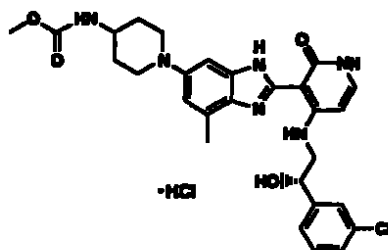
A solution of the 4-amino-piperidine compound (~ 50-100 μmol) in 5 ml MeOH is cooled to 0°C. Then ~10 equivalent of Huenigs base and ~ 3 equivalent of carbamoyl chloride are added. The vial is shaken once and allowed to stand at ambient temperature overnight. Evaporation of volatiles and purification by prep. HPLC gives
 5 the 4-carbamoyl-aminopiperidine compounds.

Example 582



10 **4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methoxyethoxycarbonyl)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one:** ^1H NMR (500 MHz, CD_3OD) δ 7.90 (1H, s), 7.26 – 7.52 (6H, m), 6.29 (1H, d, $J = 7.5$ Hz), 4.97 (1H, dd, $J = 4.1, 7.0$ Hz), 4.20 (2H, m), 3.93 (1H, m), 3.60 – 3.84 (8H, m), 3.37 (3H, s), 2.69 (3H, s), 2.33 (2H, m), 2.13 (2H, m). LCMS
 15 $(\text{M}+\text{H})^+$ m/z 595 ($t = 1.09$ min, YMC Xterra C18 S7 3.0 x 50 mm; 0 - 100% gradient over 1.5 min; 5 mL/min flow rate).

Example 583

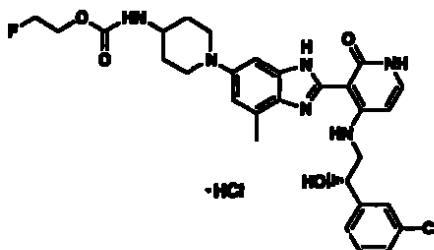


20

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(methoxycarbonyl)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ^1H NMR (500 MHz, CD_3OD) δ 8.00 (1H, s), 7.63 (1H, s), 7.26 – 7.49 (5H, m), 6.32 (1H, d, $J = 7.6$ Hz), 4.96 (1H, dd, $J = 4.2, 7.6$ Hz), 3.93 (1H, m), 3.79 – 3.88 (4H, m), 3.67 (3H, s), 3.56 – 3.65 (2H, m), 2.71 (3H, s), 2.32 (2H, m), 2.17 (2H, m). LCMS $(\text{M}+\text{H})^+$ m/z
 25

551 (t = 1.07 min, YMC Xterra C18 S7 3.0 x 50 mm; 0 - 100% gradient over 1.5 min; 5 mL/min flow rate).

Example 584



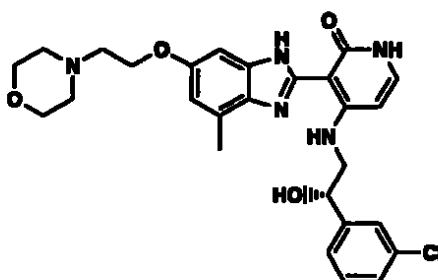
5

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroethoxy carbamoyl)- piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one: ¹H NMR (500 MHz, CD₃OD) δ 7.92 (1H, s), 7.26 – 7.54 (6H, m), 6.3 (1H, d, J = 7.5 Hz), 4.97 (1H, dd, J = 4.5, 7.5 Hz), 4.63 (1H, broad s), 4.53 (1H, d, J = 2.5 Hz), 4.32 (1H, broad s), 4.27 (1H, broad s), 3.93 (1H, m), 3.79 – 3.85 (4H, m), 3.58 – 3.72 (2H, m), 2.70 (3H, s), 2.33 (2H, m), 2.15 (2H, m). LCMS (M+H)⁺ m/z 583 (t = 1.29 min, YMC Xterra C18 S7 3.0 x 50 mm; 0 - 100% gradient over 2 min; 5 mL/min flow rate).

15

The following examples (585-590) were prepared according to Scheme VII and III and illustrate the use of an alcohol as the nucleophile in Scheme VII

Example 585 (General procedure for Examples 585-590)

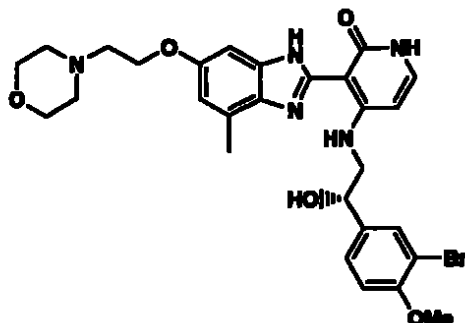


20

(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.53 (1H, s), 7.37 – 7.39 (1H, m), 7.23 – 7.30 (3H, m), 7.01 (1H, s), 6.75

(1H, s), 6.21 (1H, d, $J = 7.2$ Hz), 4.98 (1H, t, $J = 5.6$ Hz), 4.40 (2H, br s), 3.97 (4H, br s), 3.45 – 3.73 (8H, m), 2.54 (3H, s). LCMS (M+H)⁺ m/z 524 ($t = 1.24$ min.).

Example 586

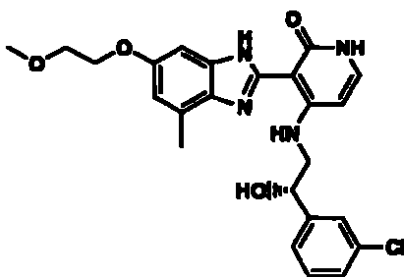


5

(*S*)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.67 (1H, narrow d, $J = 1.6$ Hz), 7.36 (1H, dd, $J = 1.6, 8.4$ Hz), 7.25 (1H, d, $J = 7.2$ Hz), 6.98 (1H, s), 6.92 (1H, d, $J = 8.4$ Hz), 6.75 (1H, s), 6.22 (1H, d, $J = 7.2$ Hz), 4.89 – 4.92 (1H, m), 4.41 (2H, br s), 3.97 (4H, br s), 3.79 (3H, s), 3.34 – 3.66 (8H, m), 2.51 (3H, s). LCMS (M+H)⁺ m/z 598 ($t = 1.22$ min.).

10

Example 587



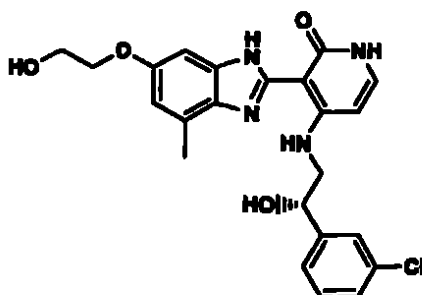
15

(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-methoxyethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.48 (1H, s), 7.25 – 7.36 (4H, m), 6.96 (1H, s), 6.81 (1H, s), 6.20 (1H, d, $J = 7.4$ Hz), 4.90 – 4.93 (1H, m), 4.13 – 4.14 (2H, m), 3.76 – 3.77 (2H, m), 3.50 – 3.61 (2H, m), 3.43 (3H, s), 2.53 (3H, s). LCMS (M+H)⁺ m/z 469 ($t = 1.52$ min.).

20

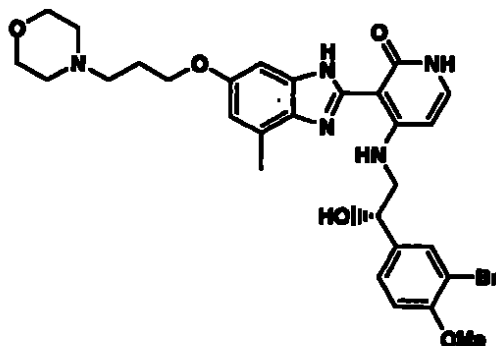
112

Example 588



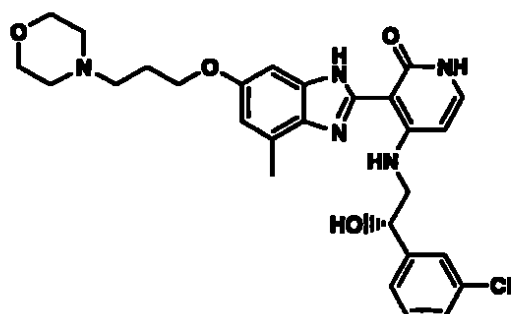
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-hydroxy-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.43 – 7.45 (2H, m), 7.27 – 7.34 (3H, m), 7.08 (1H, s), 7.04 (1H, narrow d, J = 1.0 Hz), 6.28 (1H, d, J = 7.6 Hz), 4.87 (1H, m), 4.13 (2H, t, J = 4.6 Hz), 3.92 (2H, t, J = 4.6 Hz), 3.45 – 3.54 (2H, m), 2.60 (3H, s). LCMS (M+H)⁺ m/z 455 (t = 1.35 min.).

10 Example 589



(S)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(3-morpholin-4-yl-propoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.66 (1H, s), 7.35 (1H, dd, J = 1.6, 7.9 Hz), 7.25 (1H, br s), 6.93 (1H, s), 6.91 (1H, s), 6.68 (1H, s), 6.19 (1H, br s), 4.86 (1H, m), 4.05 – 4.10 (4H, br s), 3.79 (3H, s), 3.17 – 3.73 (12H, m), 2.50 (3H, s). LCMS (M+H)⁺ m/z 612 (t = 1.16 min.).

Example 590

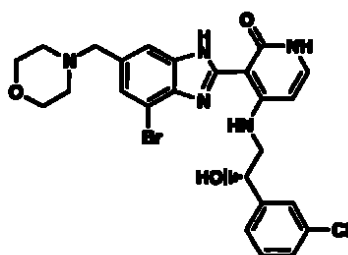


5 **(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(3-morpholin-4-yl-propoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one:** ^1H NMR (400 MHz, CD_3OD) δ 7.52 (1H, s), 7.36 – 7.38 (1H, m), 7.23 – 7.30 (3H, m), 6.92 (1H, s), 6.67 (1H, s), 6.18 (1H, d, J = 6.9 Hz), 4.96 (1H, t, J = 5.9 Hz), 4.04 – 4.08 (4H, m), 3.82 (2H, m), 3.56 – 3.65 (8H, m), 3.15 – 3.18 (2H, m), 2.52 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 538 (t = 1.19 min.).

10

The following examples (591-593) were prepared according to Scheme VII and III wherein a cyano group (Scheme IV) is converted to an aldehyde which undergo reductive amination with an amine

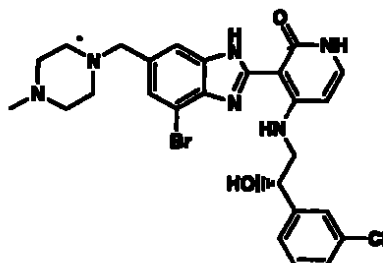
15 **Example 591 (General Procedure for Examples 591-593)**



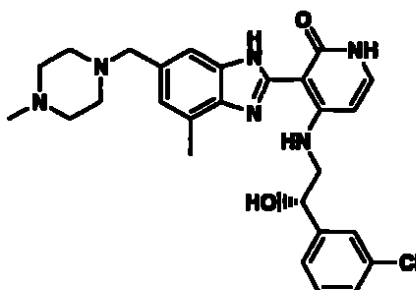
20 **(S)-3-(4-Bromo-6-morpholin-4-ylmethyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one:** To a solution of (S)-7-Bromo-2-[4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-3H-benzimidazole-5-carbaldehyde (130 mg, 0.27 mmol) in methanol (60 mL) was added morpholine (0.2 mL, excess). The reaction mixture was stirred 1 h at room temperature. Then NaCNBH_3 (1M THF solution, 1.35 mL, 1.35 mmol) was added. The reaction mixture was stirred at room temperature overnight and concentrated *in*

vacuo. The residue was purified by prep. HPLC to yield the title compound (68 mg, 45%). ¹H NMR (400 MHz, CD₃OD) δ 7.83 (1H, s), 7.69 (1H, s), 7.68 (1H, s), 7.24 - 7.54 (4H, m), 6.30 (1H, d, *J* = 7.6 Hz), 4.89 - 5.02 (1H, m), 4.50 (2H, s), 3.66 - 3.71 (4H, m), 3.17 - 3.43 (6H, m). LCMS (M+H)⁺ *m/z* 558 (*t* = 1.41 min.).

5

Example 592

(*S*)-3-[4-Bromo-6-(4-methyl-piperazin-1-ylmethyl)-1H-benzimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one: ¹H NMR (400 MHz, CD₃OD) δ 7.70 (1H, s), 7.55 (2H, s), 7.42 (1H, d, *J* = 7.6 Hz), 7.24 - 7.32 (3H, m), 6.22 (1H, d, *J* = 7.6 Hz), 5.01 (1H, t, *J* = 6.2 Hz), 4.35 (2H, br s), 3.48 - 3.71 (10H, m), 2.98 (3H, s). LCMS (M+H)⁺ *m/z* 571 (*t* = 1.37 min.).

15 **Example 593**

(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one: Through a mixture of (*S*)-3-[4-Bromo-6-(4-methyl-piperazin-1-ylmethyl)-1H-benzimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one (80 mg, 0.14 mmol), tetramethyl tin (2.5 mL, excess), PdCl₂ (PPh₃)₄ (10 mg, 0.014 mmol), and KF (40 mg, 0.7 mmol) in DMF (2 mL) in a vial was bubbled nitrogen, sealed, and heated to 100°C for two days. The reaction mixture was passed through a small pad of

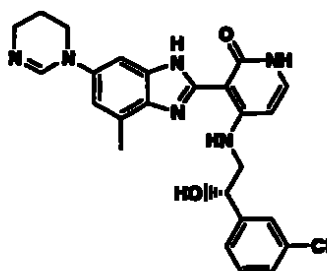
celite. After concentration, the residue was purified by prep. HPLC to give the titled compound (34 mg, 48%). ¹H NMR (400 MHz, CD₃OD) δ 7.53 (1H, s), 7.45 (1H, s), 7.24 - 7.40 (4H, m), 7.09 (1H, s), 6.22 (1H, d, *J* = 7.6 Hz), 4.99 (1H, t, *J* = 6.4 Hz), 4.04 (2H, br s), 3.61 - 3.74 (2H, m), 2.98 - 3.34 (8H, m), 2.80 (3H, s), 2.58 (3H, s).

5 LCMS (M+H)⁺ *m/z* 507 (*t* = 1.29 min.).

The following examples (594-595) were prepared according to Scheme VII and III and illustrate the use of tetrahydropyrimidine as the nucleophile in Scheme VII

10

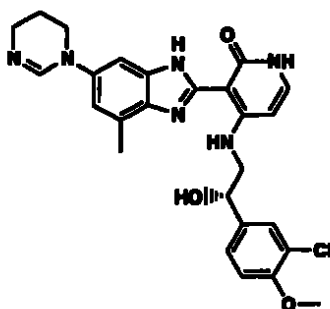
Example 594



4-[2-(3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-(1,4,5,6-tetrahydropyrimidine-1-yl)-1H-benzimidazol-2-yl]-1H-pyridine-2-one: ¹H

15 NMR (400 MHz, CD₃OD) δ 8.38 (1H, s), 7.52 (1H, s), 7.21-7.41 (5H, m), 7.04 (1H, d, *J* = 1.2 Hz), 6.21 (1H, d, *J* = 7.6 Hz), 4.97 (1H, t, *J* = 4.9 Hz), 3.97 (2H, m), 3.60-3.73 (2H, m), 3.52 (2H, t, *J* = 5.74 Hz), 2.60 (3H, s), 2.25 (2H, m). LCMS (M+H)⁺ *m/z* 477 (*t* = 1.79 min.)

20 Example 595



4-[2-(4-Methoxy-3-chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-(1,4,5,6-tetrahydropyrimidine-1-yl)-1H-benzimidazol-2-yl]-1H-pyridine-2-one:

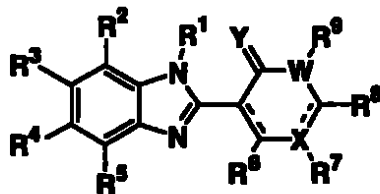
¹H NMR (400 MHz, CD₃OD) δ 8.37 (1H, s), 7.52 (1H, s), 7.04-7.52 (4H, m), 7.04 (1H, d, J = 1.2 Hz), 6.21 (1H, d, J = 7.6 Hz), 4.98 (1H, t, J = 4.92 Hz), 3.97 (5H, m), 3.60-3.73 (2H, m), 3.52 (2H, t, J = 5.74 Hz), 2.60 (3H, s), 2.26 (2H, m). LCMS (M+H)⁺ m/z 507 (t = 1.67 min.)

5

It is understood that the examples described above in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety.

What is claimed is:

1. A compound according to formula I



I

its enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs
and solvates thereof;

wherein

X is selected from the group consisting of N, C, C₁-C₃ alkyl, C₁-C₃ alkyl
substituted with one or more R⁷, and a direct bond;

Y is selected from the group consisting of O and S ;

W is selected from the group consisting of N, C, O, and S; provided that if W
is O or S, R⁹ is absent;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ are each independently selected from the
group consisting of H, C₁₋₆ alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo,
amino, OR⁶⁰, NO₂, OH, SR⁶⁰, NR⁶⁰R⁶¹, CN, CO₂R⁶⁰, CONR⁶⁰R⁶¹, OCONR⁶⁰R⁶¹,
NR⁶²CONR⁶⁰R⁶¹, NR⁶⁰SO₂R⁶¹, SO₂NR⁶⁰R⁶¹, C(NR⁶²)NR⁶⁰R⁶¹, aryl, heteroaryl,
(CH₂)_nOR⁶⁰, (CH₂)_nNR⁶⁰R⁶¹, (CH₂)_nSR⁶⁰, (CH₂)_n aryl, (CH₂)_n heteroaryl, ,
(CH₂)_n heterocycloalkyl, NH-Z-aryl, and NH-Z-heteroaryl;

wherein n is 1 to 3; and

Z is selected from the group consisting of C₁ - C₄ alkyl, alkenyl, and alkynyl
chain; Z having one or more hydroxy, thiol, alkoxy, thioalkoxy, amino, halo,
NR⁶⁰SO₂R⁶¹ groups; Z optionally incorporating one or more groups selected from the
group consisting of CO, CNOH, CNOR⁶⁰, CNNR⁶⁰, CNNCOR⁶⁰ and CNNSO₂R⁶⁰;
and

R⁶⁰, and R⁶¹ are independently selected from the group consisting of H, alkyl,

alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, heteroaryl, heteroarylalkyl, and alkyl- R^{25} wherein

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, -
 5 $NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

2. The compound according to claim 1 wherein

10 R^1 , R^7 , R^8 and R^9 are H;

R^2 and R^4 are H or F;

Y is O;

X is selected from the group consisting of N and CH;

W is N;

15 R^5 is selected from the group consisting of H, methyl, ethyl, isopropyl, secondary butyl, cyclopropyl, F, and CF_3 ;

R^6 is selected from the group consisting of H, 2-aminomethylpyridine, $NHCH_2CH(OH)Ph$, $NHCH_2CH(OH)(3-Cl-Ph)$, $NHCH_2CH(OH)(3-Br-Ph)$, $NHCH_2CH(OH)(3-Br-4-OMe-Ph)$, $NHCH(CH_2OH)CH_2Ph$, $NHCH_2CH(OH)aryl$,
 20 and $NHCH(CH_2OH)CH_2aryl$; and

R^3 is selected from the group consisting of OR^{60} , $C(NH)NHR^{60}$, $C(O)NHR^{60}$ imidazole, imidazoline, tetrahydropyrimidine, piperazine, morpholine, homomorpholine, piperidine, pyrrolidine, homopiperazine and amino; wherein

R^{60} is selected from the group consisting of H, alkyl, cycloalkyl,
 25 heterocycloalkyl, and alkyl- R^{25} wherein R^{25} is hydrogen, alkenyl, hydroxy, thiol, thioalkoxy, alkoxy, thioalkoxy, halo, cyano, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, or a heteroaryl or heterocycloalkyl; and

R_{30} and R_{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

30 3. The compound according to claim 2 wherein R^3 is $-OR^{60}$ and R^{60} is alkyl, or -alkyl- R^{25} , wherein

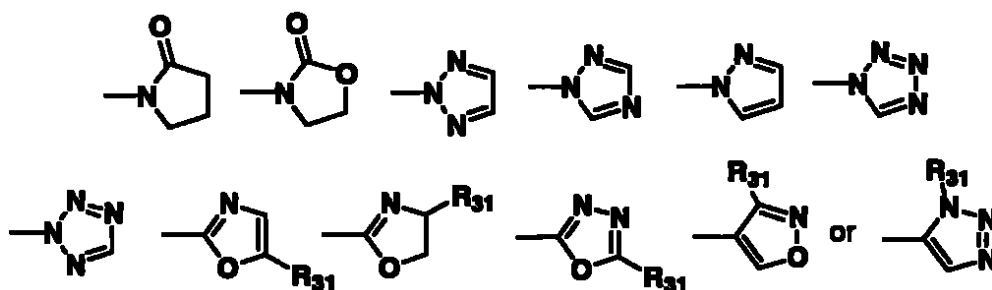
R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, cyano, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and

R_{30} and R_{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

5

4. The compound according to claim 3 wherein R^{60} is methyl, $-(CH_2)_nCH_2OH$, or $-(CH_2)_nCH_2N(CH_2CH_2)_2O$, and n is 0, 1, or 2.

5. The compound according to claim 3 wherein R^{25} is morpholine,



10

wherein R^{33} is hydrogen, alkyl, or substituted alkyl.

6. The compound according to claim 2 wherein R^3 is piperazine, homopiperazine, 3-methylpiperazine, or 3,5-dimethylpiperazine being optionally substituted at the 4-N position with a compound selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, alkyl- R^{25} , $-C(O)-R^{15}$, or $-CO_2R^{15}$ wherein R^{15} is hydrogen, alkyl, aryl, alkyl- R^{25} , amino or aryl; and

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, cyano, halo, sulfoxy, sulfonyl, arylsulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

7. The compound according to claim 6 wherein said piperazine is substituted with methyl, ethyl, CH_2 -cyclopropyl, hydroxyethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl, 2-aminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl, methoxyethyl, ethoxyethyl, morpholine, and morpholinylethyl.

8. The compound according to claim 2 wherein R^3 is an amino group selected from the group consisting of hydroxyalkylamino, aminoalkylamino, dialkylaminoalkylamino, and heterocycloalkylalkylamino.

5

9. The compound according to claim 8 wherein said amino is selected from the group consisting of $NHCH_2CH_2OH$, $NMeCH_2CH_2OH$, $NEtCH_2CH_2OH$, $NHCH_2CH_2NH_2$, $NMeCH_2CH_2NH_2$, $NEtCH_2CH_2NH_2$, $NHCH_2CH_2NMe_2$, $NMeCH_2CH_2NMe_2$, $NEtCH_2CH_2NMe_2$, $NHCH_2CH_2NEt_2$, $NMeCH_2CH_2NEt_2$, $NEtCH_2CH_2NEt_2$, $NHCH_2CH_2N(CH_2CH_2)_2O$, $NMeCH_2CH_2N(CH_2CH_2)_2O$, and $NEtCH_2CH_2N(CH_2CH_2)_2O$.

10

10. The compound according to claim 2 wherein R^3 is piperidine, optionally substituted with hydroxy, thiol, amino, alkylamino, dialkylamino, alkoxy, thioalkoxy, 1,3 dioxolane, 1,3 dioxane, $-NHC(O)R^{15}$, $-NHCO_2R^{15}$, wherein R^{15} is hydrogen, alkyl, aryl or alkyl- R^{25} wherein R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, cyano, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

20

11. The compound according to claim 2 wherein R^3 is morpholine, thiomorpholine, sulfoxymorpholine, sulfonylmorpholine, or homomorpholine, or a substituted morpholine, thiomorpholine, sulfoxymorpholine, sulfonylmorpholine, or homomorpholine.

25

12. The compound according to claim 11 wherein said morpholine, thiomorpholine, sulfoxymorpholine, sulfonyl morpholine, or homomorpholine is substituted with hydroxy, thiol, amino, alkylamino, dialkylamino, alkoxy, thioalkoxy, alkyl- R^{25} $-NHC(O)R^{15}$, $-NHCO_2R^{15}$, wherein R^{15} is hydrogen, alkyl, aryl or alkyl- R^{25} wherein R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, cyano,

30

sulfoxy, sulfonyl, $-\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}\text{C(O)R}^{31}$, $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $-\text{C(O)NR}^{30}\text{R}^{31}$, heteroaryl or heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

5 13. The compound according to claim 2 wherein R^3 is $(\text{CH}_2)_n$ -morpholine or $(\text{CH}_2)_n$ -piperazine, wherein n is 1 to 3.

14. The compound according to claim 2 wherein R^3 is an optionally substituted N-tetrahydropyrimidine or N-imidazoline.

10

15. The compound according to claim 14 wherein at least one of said substituents is alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanoalkyl, carboxyl, or carboxamide.

16. The compound according to claim 2 wherein R^3 is pyrrolidine.

15

17. The compound according to claim 2 wherein said pyrrolidine is selected from the group consisting of 3-hydroxyl pyrrolidine, 3-alkoxy pyrrolidine, and 3-alkylamino pyrrolidine, 3-dialkylamino pyrrolidine.

20 18. The compound according to claim 2 wherein R^6 is selected from the group consisting of H, 2-aminomethylpyridine, $\text{NHCH}_2\text{CH(OH)aryl}$, and $\text{NHCH}(\text{CH}_2\text{OH})\text{CH}_2\text{aryl}$.

25 19. The compound according to claim 18 wherein said aryl is an optionally substituted phenyl.

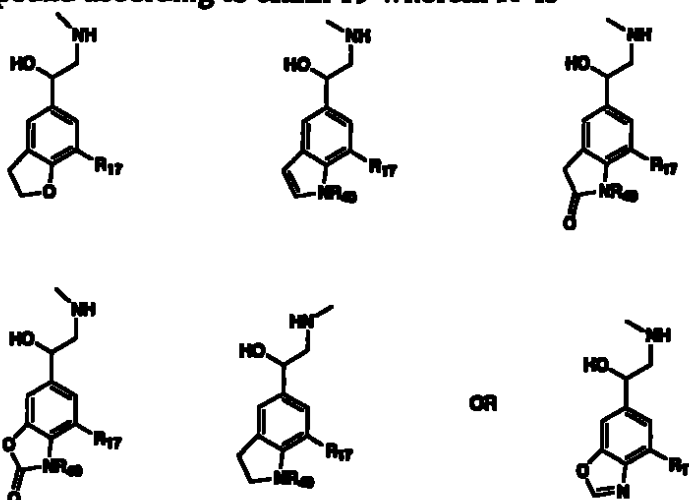
20. The compound according to claim 19 wherein said phenyl is substituted with a Br, Cl, F, alkoxy or NHSO_2CH_3 .

30 21. The compound according to claim 19 wherein said substituent is 3-Br, 3-Cl or 3-F.

117

22. The compound according to claim 19 wherein said substituent is 4-F or 4-methoxy.

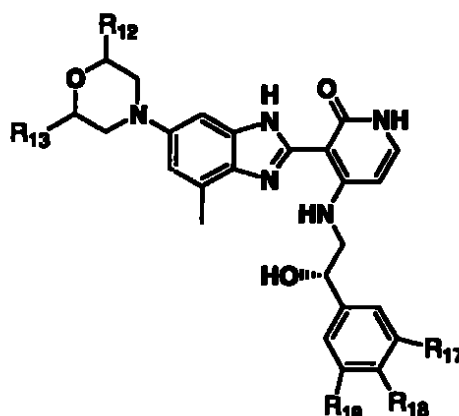
23. The compound according to claim 19 wherein R^6 is



5

wherein R^{17} is H, Br, Cl, or F and R^{40} is H or alkyl.

24. A compound having the formula:



10

wherein R^{12} and R^{13} are, independently, hydrogen, alkyl, or alkyl- R^{25} wherein

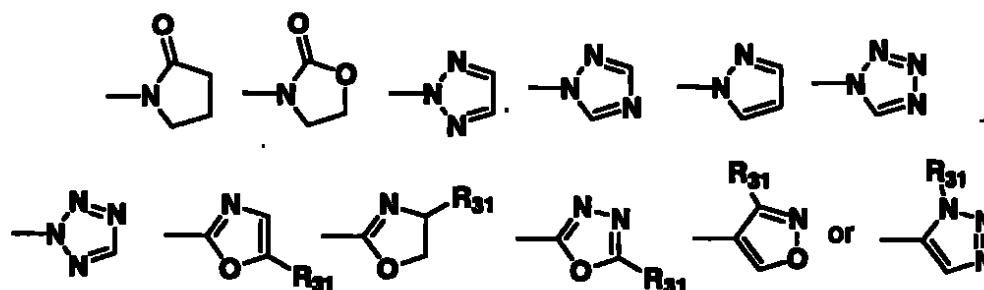
R^{25} is hydrogen, hydroxy, thiol, alkenyl, amino, alkoxy, thioalkoxy, halo, cyano, sulfoxy, sulfonyl, $-CO_2H$, $-C(O)NR^{30}R^{31}$, $-NR^{30}SO_2R^{31}$, $-NR^{30}C(O)R^{31}$, -

15 $NR^{30}C(O)OR^{31}$, heteroaryl or heterocycloalkyl;

R^{17} , R^{18} and R^{19} are, independently, hydrogen, halogen, or alkoxy, or R^{18} and R^{19} together form a heterocycloalkyl or heteroaryl group; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, or alkyl- R^{25} .

25. The compound according to claim 24 wherein R²⁵ is morpholine,

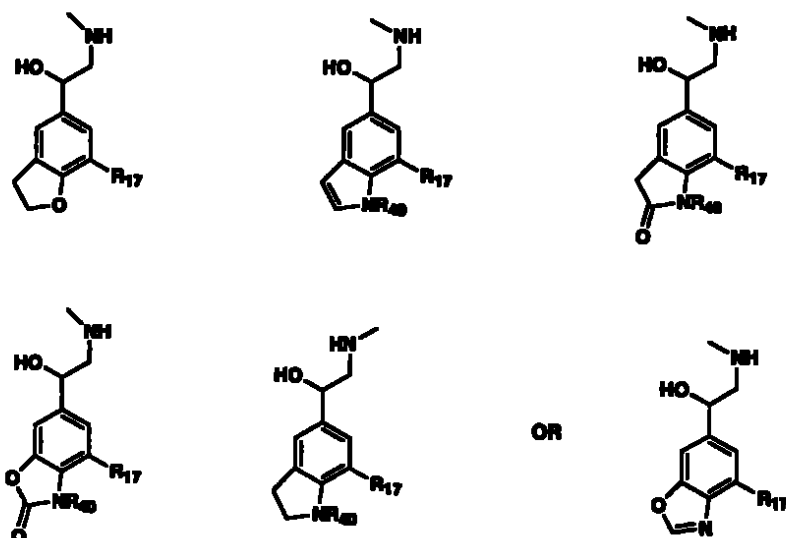


5 wherein R³³ is hydrogen, alkyl, or substituted alkyl.

26. The compound according to claim 24 wherein R¹² is hydrogen, methyl, hydroxymethyl, methoxymethyl, CH₂F, CH₂CN, CO₂H, or -CONR³⁰R³¹ wherein R³⁰ and R³¹ are, independently, hydrogen, or alkyl-R²⁵.

10

27. The compound according to claim 24 incorporating the side chain



wherein R⁴⁰ is hydrogen or alkyl, and R⁷⁰ hydrogen or halogen.

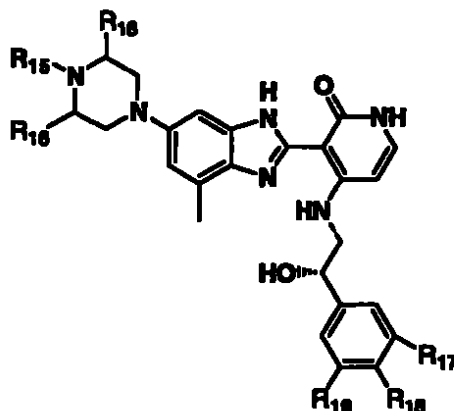
15

28. The compound according to claim 24 wherein R¹² and R¹³ are H; R¹⁷ is Br, F, or Cl; R¹⁸ is methoxy or fluoro; and R¹⁹ is H; or R¹⁸ and R¹⁹ together form 4-O, 5 dihydrofuranyl.

118

29. The compound according to claim 24 wherein R^{12} and R^{13} are methyl; R^{17} is Br, F or Cl, R^{18} is hydrogen or methoxy; and R^{19} is H.

30. A compound having the formula



5

wherein R_{15} is hydrogen, alkyl, aryl, or -alkyl- R^{25} , wherein

R^{25} is is-hydrogen, hydroxy, thiol, alkenyl, amino, alkoxy, thioalkoxy, halo, cyano, sulfoxy, sulfonyl,

$-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or

10 heterocycloalkyl;

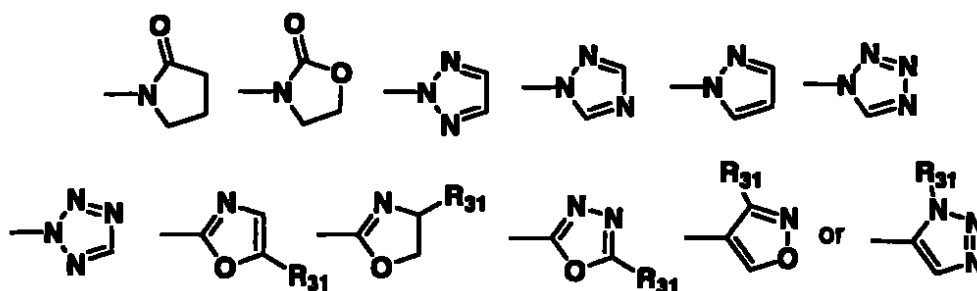
R^{16} is each independently hydrogen or methyl;

R^{17} , R^{18} and R^{19} are, independently, hydrogen, halogen, or alkoxy; or R^{18} and R^{19} together form a heterocycloalkyl or heteroaryl group; and

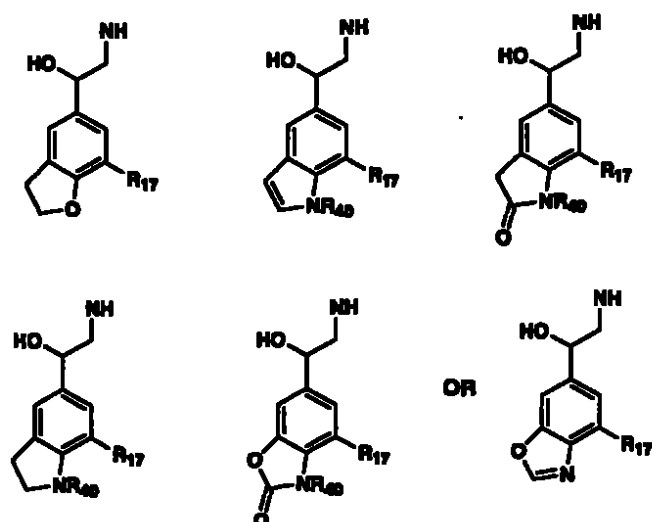
R^{30} and R^{31} are, independently, hydrogen, alkyl or alkyl- R^{25} .

15

31. The compound according to claim 30 wherein R^{25} is morpholine, thiomorpholine,



20 32. The compound according to claim 30 incorporating the sidechain

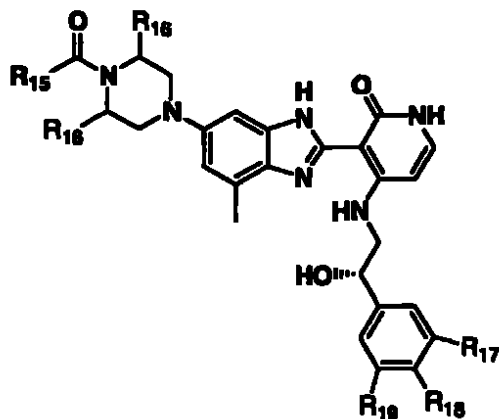


wherein R_{40} is hydrogen or alkyl and R_{17} hydrogen or halogen.

- 5 33. The compound according to claim 30 wherein R_{15} is hydrogen, methyl, ethyl, or $(\text{CH}_2)_n\text{CH}_2\text{R}_{25}$ wherein R_{25} is OH, OMe, F, CN, CF_3 , SOCH_3 or SO_2CH_3 , wherein n is 0 or 1.

- 10 34. The compound according to claim 30 wherein R_{15} is cyanoethyl, hydroxyethyl, $\text{CH}_2\text{CH}_2\text{SOCH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CN}$, or $\text{CH}_2\text{CH}_2\text{CF}_3$; R_{16} and R_{19} are H; R_{17} is Br, or Cl; and R_{18} is hydrogen or methoxy.

35. A compound having the formula:



15

wherein

R_{15} is hydrogen, alkyl, aryl or alkyl- R_{25} ;

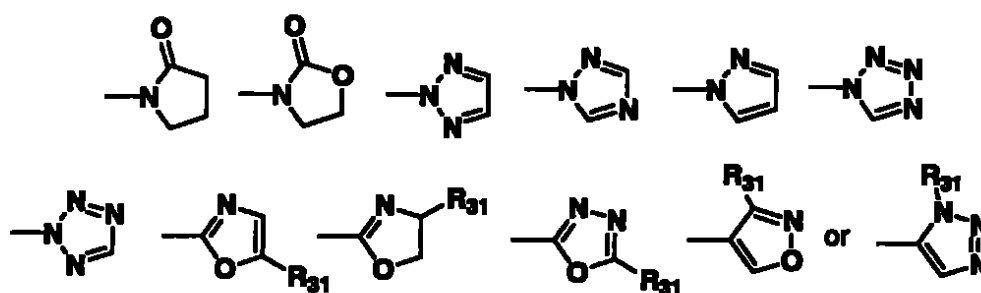
R^{25} is hydrogen, hydroxy, thiol, alkenyl, alkoxy, thioalkoxy, amino, halo, cyano, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl;

R^{16} is each independently hydrogen or methyl;

5 R^{17} , R^{18} and R^{19} are, independently, hydrogen, halogen, or alkoxy, or R^{18} and R^{19} together form a heterocycloalkyl or heteroaryl group; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl or alkyl- R^{25} .

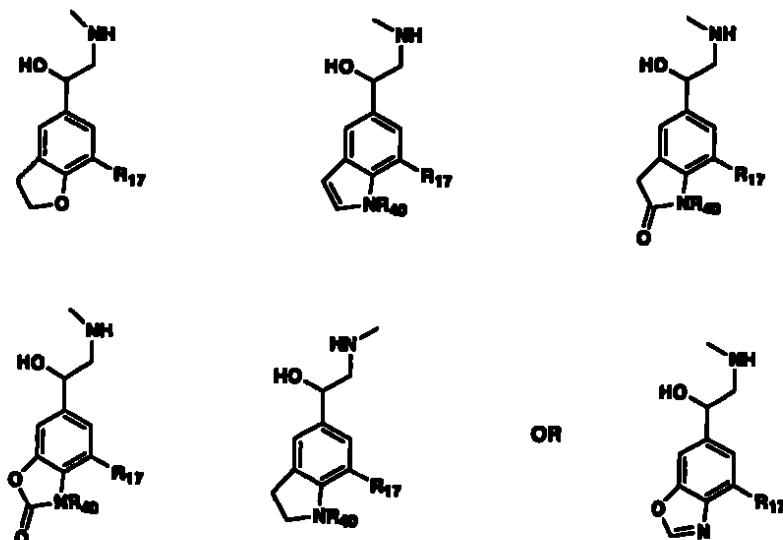
36. The compound according to claim 35 wherein R^{25} is morpholine,
10 thiomorpholine,



15

wherein R^{33} is hydrogen, alkyl, or substituted alkyl.

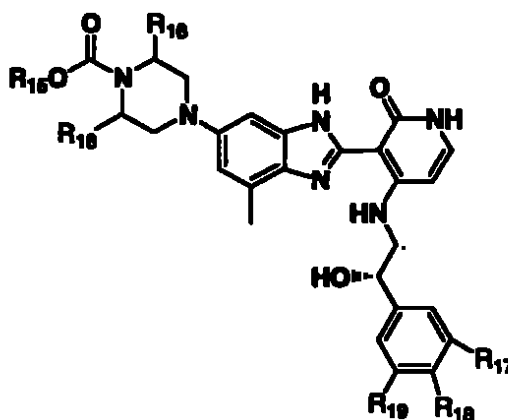
37. The compound according to claim 35 incorporating the sidechain



wherein R^{40} is hydrogen or alkyl and R^{17} hydrogen or halo.

38. The compound according to claim 35 wherein R^{15} is hydrogen or methyl; R^{17} is bromo, chloro or fluoro; R^{18} is hydrogen or methoxy; and R^{19} is hydrogen.

39. A compound having the formula



10

wherein

R_{15} is hydrogen, alkyl, or, -alkyl- R^{25} ;

R^{25} is hydrogen, hydroxy, thiol, alkenyl, alkoxy, thioalkoxy, amino, halo, cyano, sulfoxy, sulfonyl,

15 - $NR^{30}COOR^{31}$, - $NR^{30}C(O)R^{31}$, - $NR^{30}SO_2R^{31}$, - $C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl;

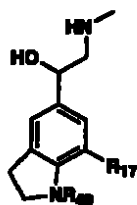
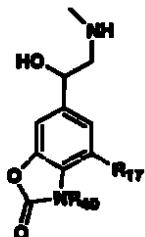
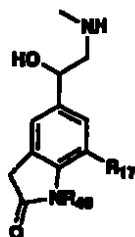
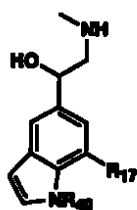
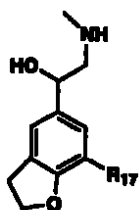
R^{16} is each independently hydrogen or methyl;

R^{17} , R^{18} and R^{19} are, independently, hydrogen, halogen, or alkoxy; or R^{18} and R^{19} together form a heterocyclo or heteroaryl group; and

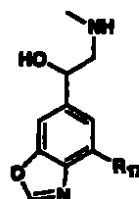
20 R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl or alkyl- R^{25} .

40. The compound according to claim 39 incorporating the sidechain

100
RD

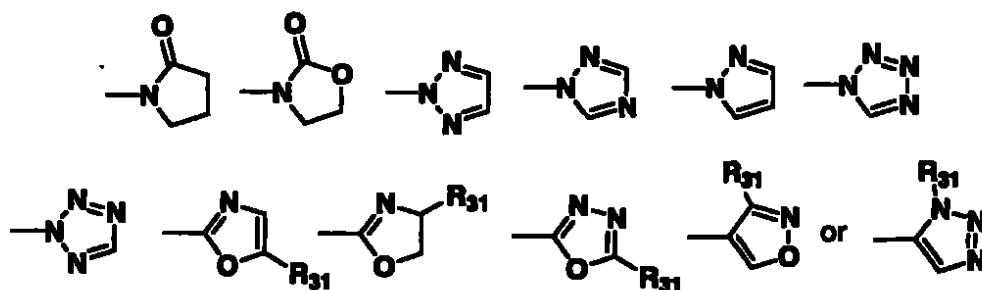


OR



wherein R^{40} is hydrogen or alkyl and R^{17} hydrogen or halo.

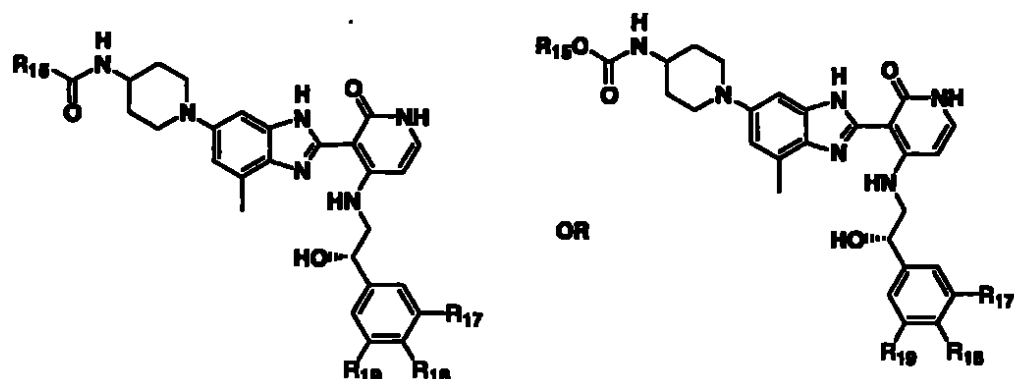
41. The compound according to claim 39 wherein R^{15} is hydrogen, methyl, ethyl, or $-(CH_2)_nCH_2-R^{25}$ wherein n is 0, 1, or 2; and R^{25} is OH, OMe, F, CN, CF_3 , $SOCH_3$, or SO_2CH_3 , $-NR^{30}COR^{31}$, $-NR^{30}COOR^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, or has the formula:



wherein R^{31} is hydrogen, alkyl, or substituted alkyl.

42. The compound according to claim 39 wherein R^{15} is ethyl, methoxyethyl, CH_2CH_2F , or CH_2CH_2CN ; R^{17} is bromo or chloro; R^{18} is methoxy or hydrogen; and R^{19} is hydrogen.

43. A compound having the formula:



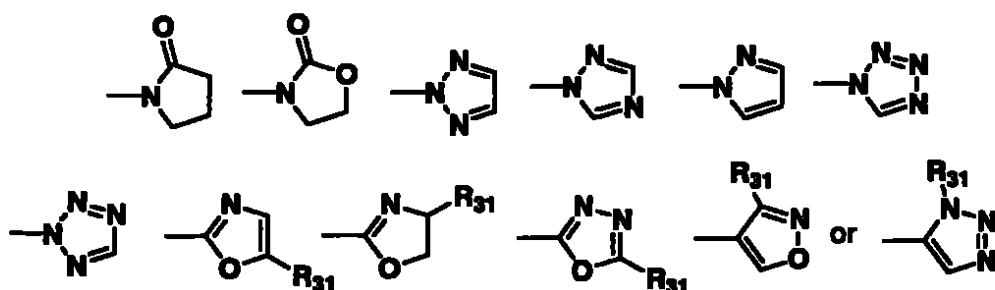
wherein

5 R_{15} is hydrogen, alkyl, aryl, or -alkyl- R^{25} ;

R^{25} is hydrogen, hydroxy, thiol, alkenyl, alkoxy, thioalkoxy, amino, halo, cyano, sulfoxy, sulfonyl, - $NR^{30}COOR^{31}$, - $NR^{30}C(O)R^{31}$, - $NR^{30}SO_2R^{31}$, - $C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl;

10 R^{17} , R^{18} and R^{19} are, independently, hydrogen, halogen, or alkoxy; or R^{18} and R^{19} together form a heterocyclo or heteroaryl group; and
 R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl or alkyl- R^{25} .

44. The compound according to claim 43 wherein R^{15} is $-(CH_2)_nCH_2R^{25}$ n is 0, 1, 2 or 3 and R^{25} is OH, OMe, F, CN, CF_3 , $SOCH_3$ or SO_2CH_3 , - $NR^{30}COOR^{31}$, -
 15 $NR^{30}C(O)R^{31}$, - $NR^{30}SO_2R^{31}$, - $C(O)NR^{31}R^{32}$ or has the formula:

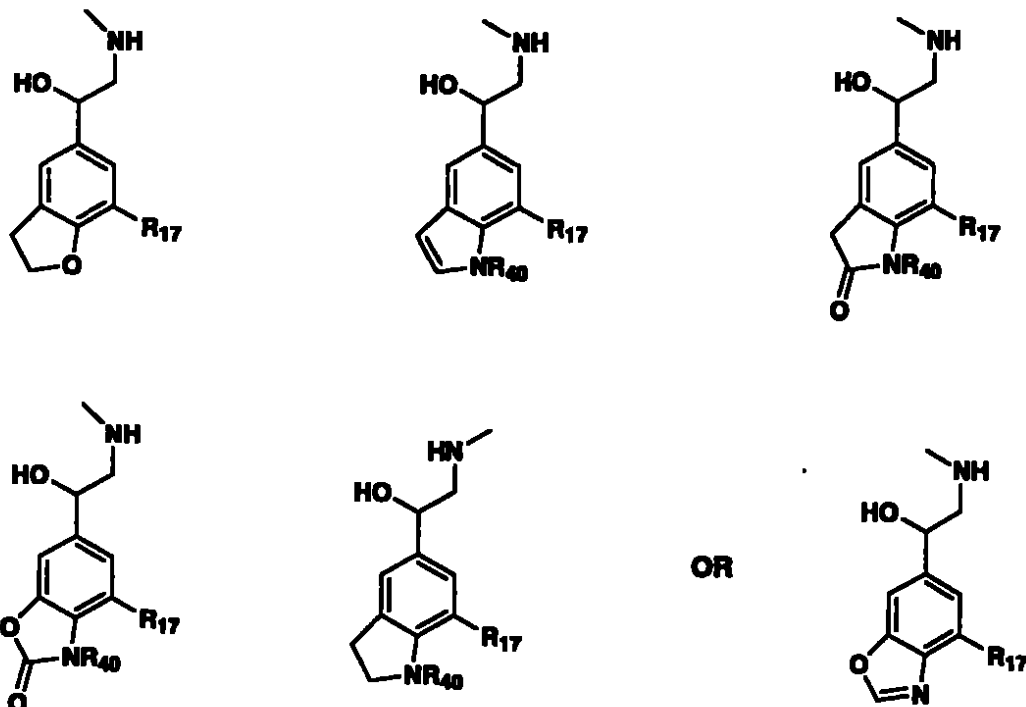


20 wherein R^{33} is hydrogen, alkyl, or substituted alkyl.

10
121

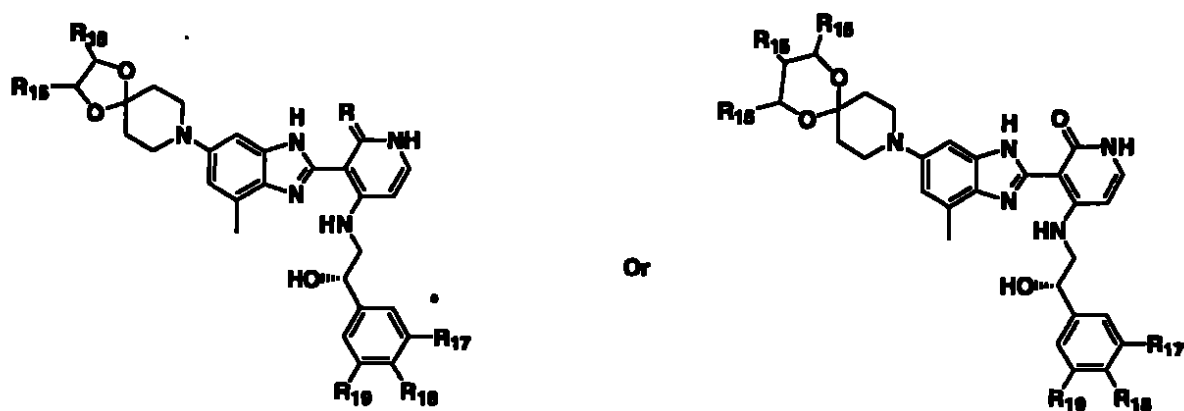
45. The compound according to claim 43 wherein R^{15} is methyl, ethyl, CH_2F , methoxyethyl, CH_2CH_2F , or $CH_2CH_2CH_2SOCH_3$; R^{17} is bromo; R^{18} is hydrogen, methoxy, or fluoro; and R^{19} is H.

5 46. The compound according to claim 45 incorporating the sidechain



wherein R^{40} is hydrogen or alkyl, and R^{17} is hydrogen or halo.

47. A compound having the formula:



wherein each R^{15} is independently hydrogen, alkyl, aryl, or -alkyl- R^{25} ;

R^{25} is hydrogen, hydroxy, thiol, alkenyl, alkoxy, thioalkoxy, amino, halo, cyano, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl;

R^{17} , R^{18} and R^{19} are, independently, hydrogen, halogen, or alkoxy; or R^{18} and R^{19} together form a heterocyclo or heteroaryl group; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl or alkyl- R^{25} .

48. The compound according to claim 1 selected from the group consisting of :

A compound according to claim 1 having the formula:

- 10 (S)-4-(2-Hydroxy-1-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-[2-Hydroxy-2-(3-iodo-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 15 (±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (S)-4-[2-(2-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 20 (S)-4-[2-(3-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (S)-4-[2-(4-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (S)-4-[2-(2-Bromo-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 25 (S)-4-[2-(3-Bromo-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-(1-Hydroxymethyl-2-pentafluorophenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 30 (S)-4-(1-Hydroxymethyl-2-pyridin-4-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

122

- (S)-4-[1-Hydroxymethyl-2-(2-naphthalenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(pyridin-2-ylmethoxy)-1H-pyridin-2-one;
- 5 (±)-4-[2-(3-Bromo-phenyl)-2-fluoro-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (S)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
- (±)-2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
- 10 (S)-2-[4-[2-(3-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
- (±)-2-[4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
- 15 (±)-2-[4-[2-(3-Fluoro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
- (±)-2-[4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
- (S)-2-[4-(2-Hydroxy-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
- 20 (±)-3-(1H-Benzimidazol-2-yl)-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- (S)-3-(1H-Benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one;
- 25 (±)-3-(1H-Benzimidazol-2-yl)-4-[2-(3-bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- (S)-4-[2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl]-piperazine-1-carboxylic acid *isopropylamide*;
- (S)-4-[2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl]-piperazine-1-carboxylic acid ethylamide;
- 30 (S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-[4-(1-phenyl-methanoyl)-piperazin-1-yl]-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

- (*S*)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[6-(4-*isopropyl*-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (*S*)-3-[6-(4-Benzyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one;
- 5 (±)-3-[6-(4-Acetyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4-*isopropyl*-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- 10 (*S*)-6-(1-Hydroxymethyl-2-phenyl-ethylamino)-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one;
- (*S*)-2-[6-Chloro-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-pyrimidin-4-ylamino]-3-phenyl-propan-1-ol;
- 15 (*S*)-4-(2-Hydroxy-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (*R*)-4-(2-Hydroxy-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (1*S*,2*R*)-4-(1-Hydroxy-indan-2-ylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 20 (±)-4-[2-Hydroxy-2-(3-hydroxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (*S*)-4-(2-Hydroxy-2-pyridin-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 25 (±)-*N*-(3-{1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-methanesulfonamide;
- (±)-4-[2-(3-Fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 30 (*S*)-4-[2-(3-Fluoro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

103
123

- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 5 (S)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (R)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 10 (±)-4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-(2-Chloro-4-{1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-carbamic acid methyl ester;
- 15 (S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(4-n-butyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-3-{6-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one;
- 20 (S)-4-{2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl}-piperazine-1-carboxylic acid amide;
- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 25 (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4-ethyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 30 (±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzimidazol-2-yl)-1H-;

- (±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 5 (±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- (±)-3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- 10 (S)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(2-morpholin-4-yl-ethylamino)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (±)-6-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one;
- 15 (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(1-hydroxy-1-methyl-ethyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (±)-3-(6-Aminomethyl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- (±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-hydroxymethyl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 20 (S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one; and
- (S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-piperidin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

25

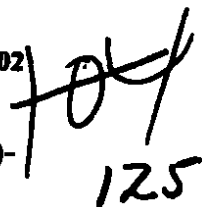
49. The compound according to claim 1 selected from the group consisting of:

- (S)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-piperidin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 4-[2-(3-Chloro-4-methylsulfanyl-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
- 30 4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl)-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

107
124

- 3-[4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazin-1-yl]-propionitrile;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 5 3-[4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-3H-benzoimidazol-5-yl)-7-methyl-piperazin-1-yl]-propionitrile;
4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid 2-fluoro-ethyl
10 ester;
4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid 2-methoxy-ethyl ester;
4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester;
15 4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid prop-2-ynyl ester;
4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid tert-
20 butyl ester;
(S)-4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carboxylic acid ethyl ester;
4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
25 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoro-ethyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
30 4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(3,3,3-trifluoro-propyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 5 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(3,4,4-trifluoro-but-3-enyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-2-hydroxy-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-2-methyl-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 10 (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- (S)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 15 [4-(2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzoimidazol-5-yl)-piperazin-1-yl]-acetonitrile;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(4-fluoro-butyryl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2,2-difluoro-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 20 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfonyl-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzoimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- 25 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-{4-[2-(1-oxo-1H-thiomorpholin-4-yl)-acetyl]-piperazin-1-yl}-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-{4-[2-(1,1-dioxo-1H-thiomorpholin-4-yl)-acetyl]-piperazin-1-yl}-4-methyl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
- 30 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(2-thiomorpholin-4-yl-acetyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;



- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-[4-(2-methanesulfinyl-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl]-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-[4-(2-methoxy-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl]-1H-pyridin-2-one;
- 5 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-[4-(2-methylsulfanyl-acetyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl]-1H-pyridin-2-one;
- 3-[6-[4-(2-Chloro-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- (*S*)-4-(2-[4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carbaldehyde;
- 10 (*S*)-4-(2-[4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carbaldehyde;
- (*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
- 15 4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
- 4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
- 4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
- 20 4-[2-(7-Bromo-2,3-dihydro-benzofuran-5-yl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl)-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-[2(*S*),6(*R*)-dimethyl-morpholine-4-yl]-1H-benzoimidazol-2-yl]-1H-pyridine-2-one;
- 25 4-[2-(3-Bromo-4-methoxy-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-[2(*S*),6(*R*)-dimethyl-morpholine-4-yl]-1H-benzoimidazol-2-yl]-1H-pyridine-2-one;
- 4-[2-(3-Chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-[6-[(*R*)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-[6-[(*S*)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- 30 4-[2-(3-Bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-[6-[(*R*)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one

and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one
5 and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(7-Bromo-2,3-dihydro-benzofuran-4-yl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one
and 4-[2-(7-bromo-2,3-dihydro-benzofuran-4-yl)-(S)-2-hydroxy-ethylamino]-3-{6-
10 [(S)-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
15 4-[2-(3-Bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one
and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
20 4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one
and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-
25 (S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
30 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

105
126

- 4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 5 4-[2-(3-Chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methoxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 10 4-[2-(3-Bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 15 4-[2-(3-Chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(R)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(S)-2-hydroxy-ethylamino]-3-{6-[(S)-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2(S)-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridine-2-one;
- 20 4-[2-(3-Bromo-4-methoxy-phenyl)-2(S)-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridine-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(acetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxyacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 25 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(acetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxyacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
- 30 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroacetamido)-piperidin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methoxyethoxycarbamoyl)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(methoxycarbamoyl)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroethoxy carbamoyl)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-methoxy-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-hydroxy-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-propoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-propoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- (S)-3-(4-Bromo-6-morpholin-4-ylmethyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- (S)-3-[4-Bromo-6-(4-methyl-piperazin-1-ylmethyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
- (S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
- 4-[2-(3-Chloro-phenyl)-2(S)-hydroxy-ethylamino]-3-[4-methyl-6-(1,4,5,6-tetrahydropyrimidine-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridine-2-one; and
- 4-[2-(4-Methoxy-3-Chloro-phenyl)-2(S)-hydroxy-ethylamino]-3-[4-methyl-6-(1,4,5,6-tetrahydropyrimidine-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridine-2-one.

50. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

106
127

51. The pharmaceutical composition according to claim 50 further comprising at least one other anti-cancer agent formulated as a fixed dose.

- 5 52. The pharmaceutical composition according to claim 51, wherein said anti-cancer agent is selected from the group consisting of: tamoxifen, toremifen, raloxifene, droloxifene, idoxifyfene, megestrol acetate, anastrozole, letrozole, borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, goserelin acetate, luprolide, finasteride, herceptin, methotrexate, 5-fluorouracil,
- 10 cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepan, vincristine, taxol, taxotere, etoposide, teniposide, amsacrine, irinotecan, topotecan, an epothilone, Iressa, OSI-774, angiogenesis inhibitors, EGF inhibitors, VEGF inhibitors, CDK inhibitors,
- 15 Her1 and Her2 inhibitors and monoclonal antibodies.

53. A method of treating a condition associated with at least one tyrosine kinase enzyme comprising administering to a mammalian species in need of such treatment an effective amount of a compound according to claim 1.

20

54. The method according to claim 53 wherein said tyrosine kinase enzyme is Abl, CDK's, EGF, EMT, FGF, FAK, Flk-1/KDR, HER-2, IGF-1R, IR, LCK, MET, PDGF, Src, or VEGF.

- 25 55. The method according to claim 53 further comprising administering to said mammalian species at least one other anti-cancer agent in combination with said compound.

56. The method according to claim 53 wherein the condition is cancer.

30

57. A method for treating cancer, comprising administering to a mammalian species in need of such treatment, a therapeutically effective amount of the composition of claim 50 or 51.
- 5 58. A method for treating proliferative diseases, comprising administering to a mammalian species in need of such treatment a therapeutically effective amount of the composition of claim 50 or 51.

107
128

INHIBIDORES DE TIROSINA CINASA NOVEDOSOS

SOLICITUDES RELACIONADAS

Esta solicitud reivindica el beneficio bajo la sección 35 U.S.C. 119 e de la solicitud de patente provisional estadounidense No. 60/279,327 presentada en marzo 28, 2001.

CAMPO DE LA INVENCION

La presente invención se relaciona de manera general con el campo de la inhibición de la enzima tirosina cinasa utilizando moléculas pequeñas novedosas.

ANTECEDENTES DE LA INVENCION

Las tirosina cinasas son una clase de enzimas, que catalizan la transferencia del fosfato terminal de la adenosina trifosfato al grupo hidroxilo fenólico de un residuo de tiroxina presente en la proteína objetivo. Las tirosinas cinasas juegan un papel crítico en la traducción de la señal de varias funciones celulares que

incluyen proliferación celular, carcinogénesis, apoptosis, y diferenciación celular (Plowman, G. D.; Ullrich, A.; Shawver, L. K.: Receptor Tyrosine Kinases As Targets For Drug Intervention. DN&P (1994) 7: 334-339). Por lo tanto los inhibidores de estas enzimas serían útiles para el tratamiento o prevención de enfermedades proliferativas que son dependientes de estas enzimas. Fuerte evidencia epidemiológica sugiere que la sobre expresión o la activación de las proteínas receptoras tirosina cinasas que conducen a señalización mitogénica constitutiva es un factor importante en el desarrollo de malignidades humanas. Las tirosina cinasas que se han implicado en estos procesos incluyen Abl, CDK's, EGF, EMT, FGF, FAK, Flk,-1/KDR, HER-2, IGF-1R, IR, LCK, MET PDGF, Src, y vega (Traxler, P. M. Protein Tyrosine Kinase Inbitors in CancerTreatmen. Exp. Opin. Ther. Patents (1997) 7: 571-588; incorporado aquí como referencia). De esta manera, existe una necesidad actual de investigar compuestos novedosos que puedan ser utilizados para regular o inhibir las enzimas de la tirosina cinasa.

RESUMEN DE LA INVENCION

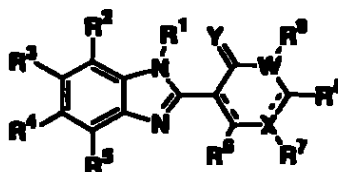
La presente invención se relaciona con compuestos que inhiben las enzimas de la tirosina cinasa,

104
130

composiciones que contengan compuestos que inhiban la tirosina cinasa y métodos de utilización de inhibidores de enzimas de tirosina cinasa para tratar enfermedades que son caracterizadas por una sobre expresión o sobre regulación de actividades de tirosina cinasa tal como cáncer, diabetes, restenosis, arteriosclerosis, psoriasis, enfermedades angiogénicas y desordenes inmunológicos (Powis, G.; Workman, P. Signaling targets For The Development of Cáncer Drugs. Anti-Cáncer Drug Design (1994), 9: 263-277; Merenmies, J.; Parada, L. F.; Henkemeyer, M. Receptor Tyrosine Kinase Signaling in Vascular Development. Cell Growth Differ (1997)8: 3-10; Shawver, L. K.; Lipsosn, K. E.; Fong, T. A. T.; McMahon, G.; Plowman, G. D.; Strawn, L. M. Receptor Tyrosine Kinase As Targets For Inhibition of Angiogenesis. Drug Discovery Today (1997)2: 50-63; todas incorporadas aquí como referencia).

Además de ser utilizado como agentes simples, se contempla que los inhibidores de tirosina cinasa puedan mejorar la actividad de tratamientos citotóxicos o citostáticos cuando se utilizan en combinación con terapias estándar conocidas en la técnica.

La presente invención está dirigida a compuestos que tienen la fórmula I



I

Sus enantiómeros, diastereómeros, sales farmacéuticamente aceptables, hidratos, prodrogas y solvatos de estos;

En donde

X se selecciona del grupo que consiste de N, C, alquilo C₁-C₃, alquilo C₁-C₃ sustituido con uno o más R⁷, y un enlace directo;

Y se selecciona del grupo que consiste de O y S;

W se selecciona del grupo que consiste de N, C, O, y S, siempre que cuando W sea O o S, R⁹ este ausente;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, son cada uno independientemente seleccionados del grupo que consiste de H, alquilo C₁-C₆, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, halo, amino, OR⁶⁰, NO₂, OH, SR⁶⁰, NR⁶⁰R⁶¹, CN, CO₂R⁶⁰, CONR⁶⁰R⁶¹, CO₂NR⁶⁰R⁶¹, NR⁶²CONR⁶⁰R⁶¹, NR⁶⁰SO₂R⁶¹, SO₂NR⁶⁰R⁶¹, C(NR⁶²)NR⁶⁰R⁶¹, arilo, heteroarilo, (CH₂)_nOR⁶⁰, (CH₂)_nNR⁶⁰R⁶¹, (CH₂)_nSR⁶⁰, (CH₂)_narilo, (CH₂)heteroarilo, (CH₂)_nheterocicloalquilo, NH-Z-arilo, y NH-Z-heteroarilo;

En donde n es 1 a 3; y

Z se selecciona del grupo que consiste de la cadena alquilo C_1-C^4 , alquenilo, y alquinilo; Z tiene uno o más grupos hidroxilo, tiol, alcoxi, tioalcoxi, amino, halo, $NR^{60}SO_2R^{61}$, Z opcionalmente incorpora uno o más grupos seleccionados del grupo que consiste de CO, CNOH, $CNOR^{60}$, $CNNR^{60}$, $CNNCOR^{60}$ y $CNNSO_2R^{60}$; y

R^{60} , R^{61} , y R^{62} son independientemente seleccionados del grupo que consiste de H, alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, hidroxilo, alcoxi, arilo, heteroarilo, heteroarilalquilo, y alquil- R^{25} en donde

R^{25} es hidrógeno, alquenilo, hidroxilo, tiol, alcoxi, tioalcoxi, amino, alquilamino, dialquilamino, arilo, heteroarilo, ciano, halo, sulfoxilo, sulfonilo, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o heterocicloalquilo, y

R^{30} y R^{31} son, independientemente, hidrogeno, alquilo, cicloalquilo, o alquil- R^{25} .

En las modalidades preferidas, R^1 , R^7 , R^8 , y R^9 son H;

R^2 y R^4 son H o F;

Y es O;

X se selecciona del grupo que consiste de N y CH;

W es N;

R^5 se selecciona del grupo que consiste de H, metilo, etilo, isopropilo, butilo secundario, ciclopropilo, F, y CF^3 ;

R^6 se selecciona del grupo que consiste de H, 2-aminoimetilpiridina, $NHCH(CH_2OH)$, CH_2ph , $NHCH_2CH(OH)arilo$, y $NHCH(CH_2OH)CH_2 arilo$; y

R^3 se selecciona del grupo que consiste de OR^{60} , $C(NH)NHR^{60}$, $C(O)NHR^{60}$ imidazol, imidazolina, tetrahidropirimidina, pirazina, morfolino, homomorfolino, piperidina, pirrolidina, homopiperazina, y amino; en donde

R^{60} se selecciona del grupo que consiste de H, alquilo, cicloalquilo, heterocicloalquilo, y alquil- R^{25} en donde R^{25} es hidrogeno, alquenilo, hidroxilo, tiol, tioalcoxi, alcoxi, tioalcoxi, halo, cano, sulfoxilo, sulfonilo, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, o un heteroarilo o heterocicloalquilo;

R_{30} y R_{31} son, independientemente, hidrógeno, alquilo, cicloalquilo, o alquil- R^{25} .

La invención también suministra una composición farmacéutica que comprende un compuesto de fórmula 1, como se definió anteriormente, y un portador farmacéuticamente aceptable.

La invención además suministra una composición farmacéutica que comprende un compuesto de fórmula I, como se definió anteriormente, en combinación con portador farmacéuticamente aceptable y al menos uno de otro agente anticanceroso opcionalmente formulado como una dosis fija.

Adicionalmente se suministra un método de tratamiento de una condición asociada con al menos una enzima de tiroxina cinasa que comprende administrar a unas especies de mamífero necesitados de tal tratamiento una cantidad efectiva de un compuesto de fórmula I como se definió anteriormente. Adicionalmente, la invención suministra un método para tratar una condición asociada con al menos una enzima de tiroxina cinasa que comprende administrar a especies de mamíferos al menos otro agente anticanceroso en combinación con un compuesto de fórmula I como se definió anteriormente.

DESCRIPCION

La presente invención suministra compuestos de fórmula I, como se definió anteriormente, composiciones farmacéuticas que emplean tales compuestos y métodos de utilización de tales compuestos.

Listadas adelante están las definiciones de varios términos utilizados para describir los compuestos de la presente invención. Esta definición aplica a los términos como ellos son utilizados a través de la especificación (a menos que ellos estén limitados de otra manera en casos específicos) o individualmente como parte de un grupo mayor.

El término "alquilo" aquí solo o como parte de otro grupo se refiere a un alcano monovalente (hidrocarburos) radical derivado que contiene de 1 a 12 átomos de carbono a menos que se defina otra cosa. Un grupo alquilo es un grupo de hidrocarburo saturado, recto, ramificado o cíclico opcionalmente sustituido. Cuando están sustituidos, los grupos alquilo pueden ser sustituidos con hasta 4 grupos sustituyentes, R como se definió, en cualquier punto disponible de unión. Cuando el grupo alquilo se dice que es sustituido con un grupo alquilo, este se utiliza intercambiabilmente con "un grupo alquilo ramificado". Ejemplos no sustituidos de tales grupos incluyen metilo, etilo, propilo, isopropilo, n-butilo, t-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetilpentilo, nonilo, decilo, undecilo, dodecilo, y similares. Sustituyentes de ejemplo pueden incluir pero no están

136

limitados a uno o más de los siguientes grupos: hidroxí, halo, (tales como F, Cl, Br, I) haloalquilo (tales como CCl_3 o CF_3), alcoxi, alquiltio, ciano, carboxi ($-\text{COOH}$), alquilcarbonilo ($-\text{C}(\text{O})\text{R}$), alcoxicarbonilo ($-\text{OCOR}$), amino, carbamoilo ($-\text{NHCOOR}$ o $-\text{OCONHR}$), urea ($-\text{NHCONHR}$), tiol, ($-\text{SH}$), sulfoxi, sulfonilo, arilo, heteroarilo, y heterocicloalquilo. Los grupos alquilo como se definieron también pueden comprender uno o más dobles enlaces carbono a carbono o uno o más triples enlaces carbono a carbono. Los grupos alquilo pueden también estar representados por la fórmula alquilo $-\text{R}^{25}$. En las modalidades preferidas, el grupo alquilo es un grupo metilo, etilo, propilo o butilo e incluye grupos metilo, etilo, propilo o butilo sustituidos.

El término "alquenilo" aquí solo o como parte de otro grupo se refiere a un radical de hidrocarburo recto, ramificado o cíclico que contiene de 2 a 12 átomos de carbono y al menos un enlace doble carbono a carbono. Un grupo alquenilo puede ser opcionalmente sustituido de la misma manera como se describió para un grupo alquilo.

El término "alquinilo" aquí solo o como parte de otro grupo se refiere a un radical hidrocarburo recto, ramificado o cíclico que contiene de 2 a 12 átomos de carbono y al menos un triple enlace carbono a carbono. Un

grupo alquínilo puede ser opcionalmente sustituido de la misma manera como se describió para un grupo alquilo.

El término "alcoxi" como se utilizó solo o en combinación se refiere aquí a un grupo alquilo de cadena recta o ramificada covalentemente unido a la molécula padre a través de una unión al átomo de oxígeno que contiene 1 a 10 átomos de carbono y los términos "alcoxi C₁₋₆" y "alcoxi inferior" se refieren a tales grupos que contienen desde uno a 6 átomos de carbono, los ejemplos incluyen, pero no están limitados a, metoxi, etoxi, propoxi, isopropoxi, butoxi, t-butoxi y similares. El término "opcionalmente sustituido" cuando se utiliza en conexión con un sustituyente alcoxi se refiere al reemplazo de hasta 2 hidrógenos, preferiblemente sobre diferentes átomos de carbono con un radical seleccionado del grupo de alquilo inferior, fenilo, ciano, halo, trifluorometilo, nitro, hidroxilo, alcanoilo, amino, monoalquilo, amino y dialquilamino. Los grupos alcoxi pueden ser sustituidos de la misma manera que los grupos alquilo pueden ser sustituidos como se describió anteriormente.

El término "sulfoxi" aquí solos como parte de un grupo se refieren a -SO y pueden ser sustituidos con, por ejemplo, grupos alquilo o arilo.

El termino "sulfonilo" aquí solos o como parte de un grupo se refieren a $-SO_2$ y pueden ser sustituidos con grupos alquilo o arilo.

El término "amino" aquí solos como parte de otros grupos se refieren a $-NH_2$. Un "amino" puede ser opcionalmente sustituido con 1 o 2 sustituyentes, que pueden ser iguales o diferentes, tales como alquilo, arilo, arilalquilo, alquenilo, alquinilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, cicloalquilo, cicloalquilalquilo, haloalquilo, hidroxialquilo, alcoxialquilo, o tioalquilo. Los sustituyentes preferidos incluyen alquilamino y dialquilamino, tal como metilamino, etilamina, dimetilamino, y dietilamino. Estos sustituyentes pueden ser adicionalmente sustituidos por un ácido carboxílico o cualquiera de los sustituyentes alquilo o arilo establecidos aquí. Además, los sustituyentes amino pueden ser tomados juntos con el átomo de nitrógeno al cual ellos están unidos para formar 1-pirrolidinilo, 1-piperodinilo, 1-azepinilo, 4-morfolinilo, 4-tiamorfolinilo, 4-sulfoximorfolino, 4-sulfonilmorfolino, 1-piperazinilo, 4-alquil-1-piperazinilo, 4-arilalquil-1-piperazinilo, 4-diarilalquil-1-piperazinilo, 1-homopiperazinilo, 4-

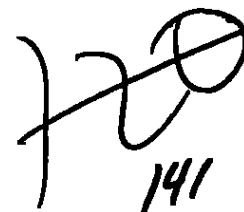
139

alquil-1-homopiperazinilo, 4, arilalquilo-1-homopiperazinilo, 4-diarilalquil-1-homopiperazinilo; 1-pirrolidinilo, 1-piperidinilo, o 1-azepinilo, opcionalmente sustituidos con alquilo, alcoxi, alquitio, halo, trifluorometilo o hidroxí.

El término "arilo" aquí solo o como parte de otro grupo se refiere a anillos aromáticos monocíclicos o bicíclicos, por ejemplo fenilo, fenilo sustituido y similares, y también grupos que están fusionados. Por ejemplo, naftilo, fenantrenilo, y similares. El grupo arilo contiene así al menos un anillo que tiene al menos 6 átomos, con hasta 5 de tales anillos estando presentes, conteniendo hasta 22 átomos allí, con enlaces dobles alternantes (resonantes) entre átomos de carbono adyacente o heteroátomos adecuados. Los grupos arilo pueden opcionalmente ser sustituidos con uno más grupos, incluyendo pero no limitados a halógeno, alquilo, alquenilo, alquinilo, alcoxi, hidroxí, carboxi, carbamoilo, alquiloxicarbonilo, alquilaminocarbonilo, nitro, trifluorometilo, aminos, cicloalquilo, ciano, alquil S(O)_n (n=0, 1, 2), o tiol. Los grupos arilo también pueden ser sustituidos con grupos heterocicloalquilo y heterocicloarilo para formar anillos fusionados, tales como dihidrobenzofuranilo, oxindolilo,

indolilo, indolinilo, oxindolilo, benzoxazolidinonilo, benzoxazolinilo, y benzoxazolidinona.

El termino "cicloalquilo" aquí solo o como parte de otro grupo se refiere a anillos de hidrocarburo completamente saturados o parcialmente saturados de 3 a 9, preferiblemente 3 a 7 átomos de carbono. Además, un cicloalquilo puede ser sustituido. Un cicloalquilo sustituido se refiere a tales anillos que tienen uno dos o tres, sustituyentes, preferiblemente uno, seleccionado del grupo que consiste de halo, alquilo, alquilo sustituido, alquenilo alquinilo, nitro, ciano, oxo(=O), hidroxilo, alcoxi, tioalquilo, $-\text{CO}_2\text{H}$, $-\text{OC}(=\text{O})\text{H}$, CO_2 -alquilo, $-\text{OC}(=\text{O})$ alquilo, $=\text{N}-\text{OH}$, $=\text{N}-\text{O}$ -alquilo, arilo, heteroarilo, heterociclo, un cetal de 5 o 6 miembros (es decir 1,3-dioxolano o 1,3-dioxano), $-\text{NR}'\text{R}''$, $-\text{C}(=\text{O})\text{NR}'\text{R}''$, $-\text{OC}(=\text{O})\text{NR}'\text{R}''$, $-\text{NR}'\text{CO}_2\text{R}''$, $-\text{NR}'\text{C}(=\text{O})\text{R}''$, $-\text{SO}_2\text{NR}'\text{R}''$, Y $-\text{NR}'\text{SO}_2\text{R}''$, en donde cada uno de R' y R'' es independientemente seleccionado de hidrógeno, alquilo, alquilo sustituido y cicloalquilo, o R' y R'' juntos forman un anillo heterociclo o heteroarilo. Los grupos cicloalquilo pueden también ser sustituidos con heteroátomos tales como O, N, y S para formar grupos heterocicloalquilo. Los grupos heterocicloalquilo preferidos incluyen opcionalmente morfolino sustituido homomorfolino (anillo de 7 miembros), tiomorfolino,



piperazina, homopiperazina, (anillo de 7 miembros), y piperidina.

El término "heteroarilo" aquí solo o como parte de otro grupo se refiere a grupos monocíclicos de 5 o 6 miembros aromáticos sustituidos y no sustituidos, grupos bicíclicos de 9 o 10 miembros, o grupos tricíclicos de 11 a 14 miembros que tienen al menos un heteroátomo (O, S o N) en al menos uno de los anillos. Cada anillo del grupo de heteroarilo que contiene un heteroátomo puede contener uno o dos átomos de oxígeno o de azufre y/o de 1 a 4 átomos de nitrógeno siempre y cuando el número total de heteroátomos en cada anillo sea 4 o menos y cada anillo tenga al menos un átomo de carbono. Los anillos fusionados que completan los grupos bicíclicos y tricíclicos pueden contener solo átomos de carbono y pueden ser saturados, parcialmente saturados o insaturados. Los átomos de nitrógeno y azufre pueden opcionalmente ser oxidados y los átomos de nitrógeno pueden opcionalmente ser cuaternarizados. Los grupos heteroarilo que son bicíclicos o tricíclicos deben incluir al menos un anillo completamente aromático pero el otro anillo fusionado o anillos pueden ser aromáticos o no aromáticos. El grupo heteroarilo puede estar unido a cualquier átomo de nitrógeno o carbono disponible de cualquier anillo. El sistema de anillo heteroarilo puede

Handwritten signature
142

contener cero, uno, dos, o tres sustituyentes seleccionados del grupo que consiste de halo, alquilo, alquilo sustituido, alqueno, alquino, nitro, ciano, hidroxilo, alcoxi, tioalquilo, $-\text{CO}_2\text{H}$, $-\text{OC}(=\text{O})\text{H}$, CO_2 -alquilo, $-\text{OC}(=\text{O})$ alquilo, fenilo, benzilo, feniletilo, feniloxi, feniltio, cicloalquilo, cicloalquilo sustituido, heterociclo, heteroarilo, $-\text{NR}'\text{R}''$, $-\text{C}(=\text{O})\text{NR}'\text{R}''$, $-\text{OC}(=\text{O})\text{NR}'\text{R}''$, $-\text{NR}'\text{CO}_2'\text{R}''$, $-\text{NR}'\text{C}(=\text{O})\text{R}''$, $-\text{SO}_2\text{NR}'\text{R}''$, Y $-\text{NR}'\text{SO}_2'\text{R}''$, en donde cada uno de R' y R'' es independientemente seleccionado de hidrógeno, alquilo, alquilo sustituido, y cicloalquilo, o R'' y R'' juntos forman un anillo heterociclo o heteroarilo.

Grupos de heteroarilo monocíclicos de ejemplo incluyen pirrolilo, pirrolidinilo, imidazolinilo, pirazolilo, pirazolinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, furanilo, tienilo, oxadiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, y similares.

Grupos heteroarilo bicíclicos de ejemplo incluyen indolilo, indolinilo, oxindolilo, benzoxazolidinona, benzotiazolilo, benzodioxolilo, benzoxazolilo, benzotienilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopirranilo, indolizininilo, benzofuranilo, cromonilo, coumarinilo,

benzopiraniilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihidroisoindolilo, tetrahidroquinolinilo y similares.

Grupos heteroarilos triciclicos de ejemplo incluyen carbazolilo, benzindolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo, y similares.

El término "halógeno" o "halo" aquí solo o como parte de otros grupos se refiere a cloro, bromo, fluor o yodo seleccionado de una manera independiente.

El término "hidroxi" aquí solo o como parte de otros grupos se refiere a -OH.

El término "tioalcoxi" aquí solo o como parte de otro grupo se refiere a un grupo alquilo como se definió aquí unido al grupo molecular padre a través de un átomo de azufre. Ejemplos de tioalcoxi incluyen, pero no están limitados a, tiometoxi, tioetoxi, y similares.

Abreviaturas: "Ph" representa fenilo; "Me" representa metilo; y "Et" representa etilo.

Un "agente anticanceroso" como se utiliza aquí incluye tratamientos anticancerosos conocidos tales como

F-203
144

terapia de irradiación o con agentes citostáticos o citotóxicos, tales como por ejemplo, pero no limitados a, agentes interactivos de ADN, tales como cisplatina o doxorubicina, Inhibidores de topoisomerasa II, tales como etoposido; inhibidores de topoisomerasa I tales como CPT-11 o topotecano; agentes interactuantes de tubulina, tales como paclitaxel, docetaxel, o las epotilonas; agentes hormonales, tales como tamoxifeno; inhibidores de timidilato sintasa, tales como 5-fluorouracil; anti-metabolitos, tales como metotrexato, inhibidores de tirosina cinasa tales como Iressa y OSI-774; inhibidores de angiogénesis; inhibidores de EGF; inhibidores de VEGF, inhibidores de CDK; inhibidores de Her1/2 y anticuerpos monoclonales dirigidos contra receptores del factor de crecimiento tales como erbitux (EGF) y herceptina (Her2).

Cuando un grupo funcional se denomina "protegido", esto significa que el grupo está en forma modificada para precluir las reacciones colaterales indeseables en el sitio protegido. Los grupos protectores adecuados para los compuestos de la presente invención se reconocerán de la presente solicitud tomando en cuenta el nivel de experticio, y con referencia a los textos estándar, tales como Greene, T. W. et al., Protective Groups in Organic Synthesis, Wiley, N. Y. (1991).

124
145

Cuando el alquilo C_{1-6} , alquenilo, alquinilo, cicloalquilo son sustituidos, ellos son preferiblemente sustituidos con uno o más hidroxil, ciano, carbamoilo, hidroxil, alcoxi, tiol, alquenilo, tioalcoxi, amino, alquilamino, amido, sulfonilo, sulfoxil, sulfonamido, halo, heterocicloalquilo, arilo o heteroarilo.

Cuando el arilo o heteroarilo son sustituidos, ellos son preferiblemente sustituidos con uno o más alquilo, alquenilo, alquinilo, ciano, carbamoilo, hidroxil, alcoxi, tioalcoxi, amino, amido, sulfonamido, halo o con R' , R'' en donde R' , R'' forman un anillo que esta fusionado al grupo arilo. Cuando CH_2 arilo o heteroarilo son sustituidos, ellos son preferiblemente sustituidos con uno más alquilo, alquenilo, alquinilo, ciano, carbamoilo, hidroxil, alcoxi, tioalcoxi, amino, amido, sulfonamido, o alógeno.

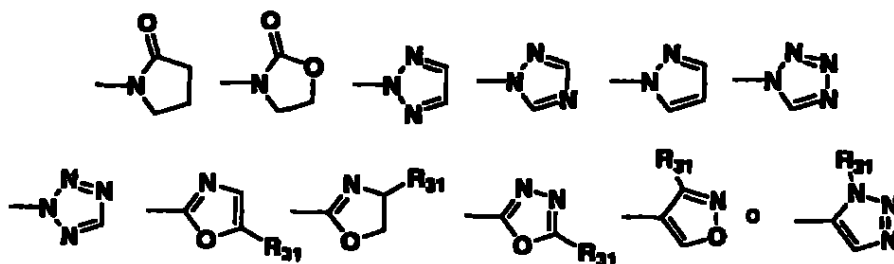
Cuando los grupos $NH-Z$ -arilo o $NH-Z$ -heteroarilo son sustituidos ellos son preferiblemente sustituidos con uno o más alquilo, alquenilo, alquinilo, hidroxil, alcoxi, tioalcoxi, amino, halógeno, nitro, nitrilo, carboxilato, alcóxicarbonilo, carbamoilo, éster, amida, arilo, o heteroarilo.

125
146

Los números en el subíndice después del símbolo "C" definen el número de átomos de carbono que un grupo particular puede contener. Por ejemplo "alquilo C₁₋₆" significa una cadena de carbono saturada recta ramificada de 1 a 6 átomos de carbono; los ejemplos incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, sec-butilo, isobutilo, t-butilo, n-pentilo, sec-pentilo, isopentilo, y n-hexilo. Dependiendo del contexto "alquilo C₁₋₆" también se puede referir a alquilenos C₁₋₆ que puentean dos grupos; ejemplos incluyen propano -1,3-diilo, butano-1,4-diilo, 2-metil-butano-1,4-diilo etc. "alqueno C₂₋₆" significa una cadena de carbono recta o ramificada que tiene al menos un doble enlace carbono-carbono, y que tiene de 2 a 6 átomos de carbono; los ejemplos incluyen etenilo, propenilo, isopropenilo, butenilo, isobutenilo, pentenilo, y hexenilo. Dependiendo del contexto, "alqueno C₂₋₆" también se puede referir a alcanodiilos, C₂₋₆ que puentean dos grupos; ejemplos incluyen etileno -1,2-diilo (vinileno), 2-metil-2-buten-1,4-diilo, 2-hexano-1,6-diilo, etc. "alquino C₂₋₆" significa una cadena de carbono recta o ramificada que tiene al menos un enlace triple carbono-carbono, y de 2 a 6 átomos de carbono; los ejemplos incluyen etinilo, propinilo, butinilo y hexinilo.

126
147

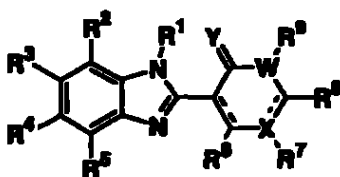
El término "alquilo- R^{25} " incluye opcionalmente grupos alquilo sustituidos tales como metilo, etilo, propilo, y butilo, unidos a un grupo R^{25} . R^{25} incluye generalmente Hidrógeno, alquenilo, hidroxilo, tiol, alcoxi, tioalcoxi, amino, alquilamino, dialquilamino, arilo, eteroarilo, ciano, halo, sulfoxi, sulfonilo, $-NHCOOH$, $-NHC(O)-$, $-NHSO_2-$, $-C(O)NH_2$, grupos heteroarilo o heterocicloalquilo tales como morfolinilo o grupos que tienen la fórmula:



Los términos "imidazol" y imidazolina" aquí solos o como parte de otro grupo incluyen imidazoles sustituidos y imidazolinias sustituidas. Similarmente, el término "tetrahidropirimidina" incluye tetrahidropirimidina sustituidas. De manera similar los términos "piperazina", "piperidina", "morfolino", "homopiperazinas", "homomorfolino" y "pirolidina" incluyen piperazinas sustituidas, piperidinas sustituidas, morfolinos sustituidos, homomorfolinos sustituidos y pirrolidinas sustituidas, respectivamente.

177
148

Los compuestos de la presente invención tienen la fórmula general I



I

Sus enantiomeros, diastereomeros, sales farmacéuticamente aceptables, hidratos, prodrogas y solvatos de estos,

En donde

X se selecciona del grupo que consiste de N, C, alquilo C₁-C₃, alquilo C₁-C₃ sustituido con uno o más R⁷, y un enlace directo;

Y se selecciona del grupo que consiste de O y S;

W se selecciona del grupo que consiste de N, C, O, y S, siempre que cuando W sea O o S, R⁹ este ausente;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, son cada uno independientemente seleccionados del grupo que consiste de H, alquilo C₁-C₆, alquenoilo, alquinoilo, cicloalquilo, heterocicloalquilo, halo, amino, OR⁶⁰, NO₂, OH, SR⁶⁰, NR⁶⁰R⁶¹, CN, CO₂R⁶⁰, CONR⁶⁰R⁶¹, CO₂NR⁶⁰R⁶¹, NR⁶²CONR⁶⁰R⁶¹, NR⁶⁰SO₂R⁶¹, SO₂NR⁶⁰R⁶¹, C(NR⁶²)NR⁶⁰R⁶¹,

127
149

arilo, heteroarilo, $(CH_2)_nOR^{60}$, $(CH_2)_nNR^{60}R^{61}$, $(CH_2)_nSR^{60}$,
 $(CH_2)_narilo$, $(CH_2)heteroarilo$, $(CH_2)_nheterocicloalquilo$,
 NH-Z-arilo, y NH-Z-heteroarilo;

En donde n es 1 a 3; y

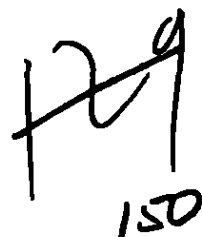
Z se selecciona del grupo que consiste de la cadena
 alquilo C_1-C_4 , alquenilo, y alquinilo; Z tiene uno o más
 grupos hidroxil, tiol, alcoxi, tioalcoxi, amino, halo,
 $NR^{60}SO_2R^{61}$, Z opcionalmente incorpora uno o más grupos
 seleccionados del grupo que consiste de CO, CNOH, $CNOR^{60}$,
 $CNNR^{60}$, $CNNCOR^{60}$ y $CNNSO_2R^{60}$; y

R^{60} , R^{61} , y son independientemente seleccionados del
 grupo que consiste de H, alquilo, alquenilo, alquinilo,
 cicloalquilo, cicloalquilalquilo, hidroxil, alcoxi, arilo,
 heteroarilo, heteroarilalquilo, y alquil- R^{25} en donde

R^{25} es hidrógeno, alquenilo, hidroxil, tiol, alcoxi,
 tioalcoxi, amino, alquilamino, dialquilamino, arilo,
 heteroarilo, ciano, halo, sulfoxil, sulfonilo, $-NR^{30}COOR^{31}$,
 $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o
 heterocicloalquilo, y

R^{30} y R^{31} son, independientemente, hidrógeno,
 alquilo, cicloalquilo, o alquil- R^{25} .

En algunas modalidades de la presente invención, R^3
 es-o R^{60} . R^{60} es alquilo, o-alquil- R^{25} , donde R^{25} es



hidrógeno, alqueno, hidroxilo, tiol, alcoxi, tioalcoxi, amino, halo, ciano, alquilsulfoxilo, alquilsulfonilo, $-R^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o heterocicloalquilo; y R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo, o alquilo- R^{25} . En las modalidades preferidas R^{60} es metilo $-(CH_2)_nCH_2OH$, o $-(CH_2)_nCH_2N(CH_2CH_2)_2O$, y n es 0, 1, o 2.

En algunas modalidades, R^3 es piperazina, homopiperazina, 3-metilpiperazina, o 3,5-dimetilpiperazina siendo opcionalmente sustituida en la posición 4-N con un compuesto seleccionado del grupo que consiste de alquilo, arilo, cicloalquilo, cicloalquilalquilo, heterocicloalquilo, alquil- R^{25} , $-C(O)-R^{15}$, o $-CO_2R^{15}$ donde R^{15} es hidrógeno, alquilo, arilo, alquil- R^{25} , amino, o arilo; R^{25} es hidrógeno, alqueno, hidroxilo, tiol, alcoxi, tioalcoxi, amino, alquilamino, dialquilamino, ciano, halo, sulfoxilo, sulfonilo, arilsulfonilo, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o heterocicloalquilo y R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo, o alquil- R^{25} . En modalidades preferidas, la piperazina es sustituida con Me, CH_2 ciclopropilo, $CH_2CH_2NMe_2$, $CH_2CH_2Net_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe , CH_2CH_2NHet , $N-CH_2CH_2N(CH_2CH_2)_2O$, $(CH_2)_nCH_2-R^{25}$ en donde R^{25} es OH, OMe, F, CN, CF_3 , $SOCH_3$ o SO_2CH_3 , en donde n es 0, 1, o 2.

130
151

En algunas modalidades, R^3 es un grupo amino. Los grupos aminos preferidos incluyen $NHCH_2CH_2OH$, $NMeCH_2CH_2OH$, $NEtCH_2CH_2OH$, $NHCH_2CH_2NH_2$, $NMeCH_2CH_2NH_2$, $NEtCH_2CH_2NH_2$, $NHCH_2CH_2NMe_2$, $NMeCH_2CH_2NMe_2$, $NEtCH_2CH_2NMe_2$, $NHCH_2CH_2NEt_2$, $NMeCH_2CH_2NEt_2$, $NEtCH_2CH_2NEt_2$, $NHCH_2CH_2N(CH_2CH_2)_2O$, $NMeCH_2CH_2N(CH_2CH_2)_2O$, $NEtCH_2CH_2N(CH_2CH_2)_2O$.

En algunas modalidades, R^3 es una piperidina opcionalmente sustituida. Los sustituyentes preferidos se seleccionan del grupo que consiste de hidroxil, tiol, amino, alquilamino, dialquilamino, alcoxi, tioalcoxi, 1,3-dioxolano $(-OCHR^{15})_2$, 1,3 dioxano $(-OCHR^{15}CHR^{15}CHR^{15}O-)-NC(O)R^{15}$, $-NHCO_2R^{15}$, donde R^{15} es hidrógeno, alquilo o alquil- R^{25} donde R^{25} es hidrógeno, alquilo, hidroxil, tiol, alcoxi, tioalcoxi, amino, halo, ciano, alquilsulfoxi, alquilsulfonilo, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo, o heterocicloalquilo; y R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo, o alquil- R^{25} .

En algunas modalidades R^3 es un morfolino opcionalmente sustituido, homomorfolino, tiomorfolino, sulfoximorfolino, o sulfonilmorfolino. Los sustituyentes preferidos incluyen hidroxil, tiol, amino, alquilamino, dialquilamino, alcoxi, tioalcoxi, alquil- R^{25} , $-NHC(O)R^{15}$, -

131
152

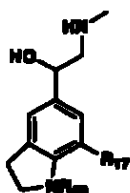
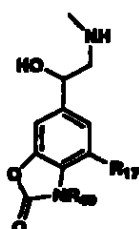
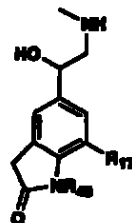
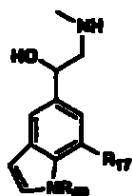
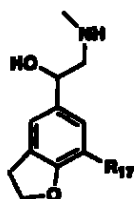
$\text{NHCO}_2\text{R}^{15}$, en donde R^{15} es hidrógeno, alquilo o alquil- R^{25} en donde R^{25} es hidrógeno, alquenilo, hidroxil, tiol, alcoxi, tioalcoxi, amino, halo, ciano, alquilsulfoxi, alquilsulfonilo, $-\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}\text{C}(\text{O})\text{R}^{31}$, $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $-\text{C}(\text{O})\text{NR}^{30}\text{R}^{31}$, heteroarilo o heterocicloalquilo; y R^{30} y R^{31} son independientemente, hidrógeno, alquilo, cicloalquilo, o alquil- R^{25} .

En algunas modalidades R^3 es pirrolidina. Las pirrolidinas preferidas incluyen, 3-hidroxil pirrolidina, 3-alcoxi pirrolidina, y 3-alquilamino pirrolidina.

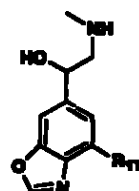
De acuerdo c a una modalidad de la presente invención, R^3 es una N-tetrahidropirimidina opcionalmente sustituida o N-imidazolina en donde los sustituyentes son, preferiblemente, alquilo, hidroxialquilo, alcoxialquilo, haloalquilo, cianoalquilo, carboxilo, o carboxamida.

En algunas modalidades, R^6 se selecciona del grupo que consiste de H, 2-aminometilpiridina, $\text{NHCH}_2\text{CH}(\text{OH})\text{arilo}$, y $\text{NHCH}(\text{CH}_2\text{OH})\text{CH}_2\text{arilo}$, en donde el grupo arilo es opcionalmente sustituido. En las modalidades preferidas, el grupo arilo es sustituido con Br, Cl, F, o metoxi. En algunas modalidades, R^6 tiene una de las siguientes fórmulas:

132
153



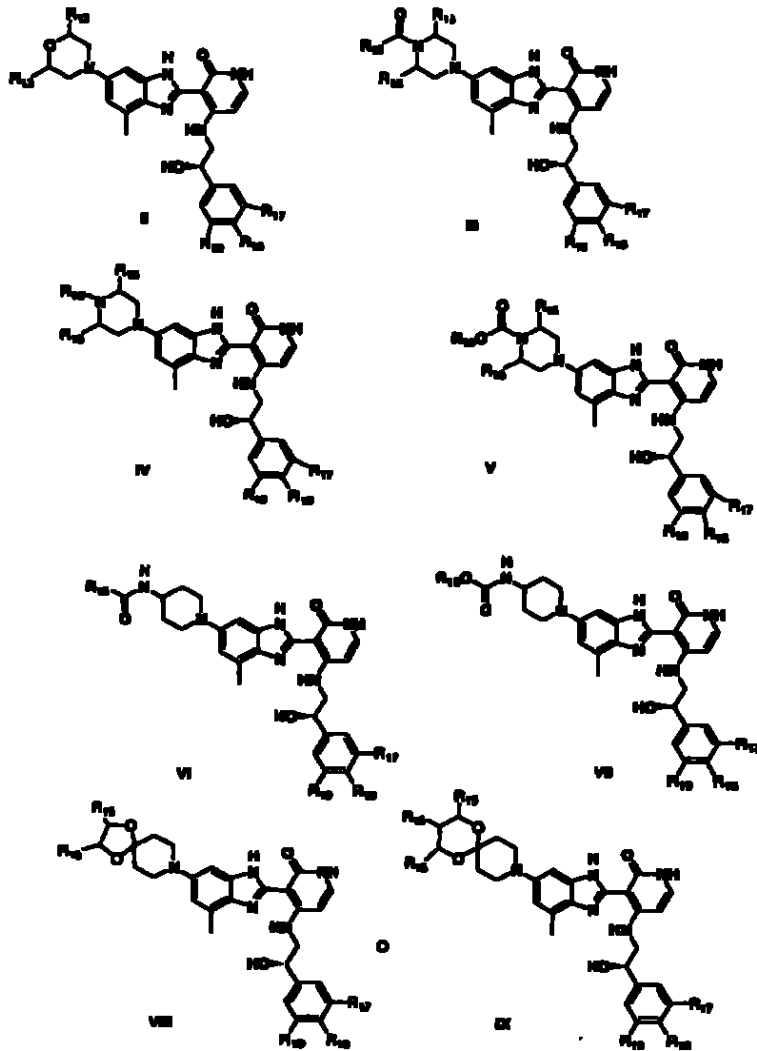
o



En donde R^{10} es hidrogeno o alquilo, preferiblemente metilo, y R^{17} es hidrógeno o halógeno, tal como Br, Cl o F.

Los compuestos preferidos de la presente invención tienen una de las siguientes fórmulas:

154



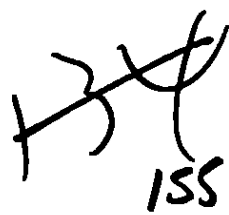
En donde

R¹² y R¹³ son independientemente, hidrógeno, alquilo, o alquil-R²⁵;

R¹⁵ es hidrógeno, alquilo, o alquil-R²⁵;

R¹⁶ es independientemente, hidrógeno o metilo;

R¹⁷, R¹⁸, y R¹⁹ son, independientemente, hidrógeno, halógeno, o alcoxi, o R¹⁸ y R¹⁹ juntos forman un grupo heterocicloalquilo o heteroarilo;



R^{25} es hidrógeno, hidroxitiol, alquenilo, alcoxi, tioalcoxi, amino, halo, ciano, sulfoxi, sulfonilo, $NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO^2R^{31}$, $-C(O)NR^{30}R_{31}$, heteroarilo o heterocicloalquilo; Y

R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo o alquil- R^{25} .

En las modalidades preferidas, R^{12} es hidrógeno, metilo, hidroximetilo, metoximetilo, CH_2F , CH_2CN , CO_2H , O $-CONR_{30}R_{31}$ en donde R^{30} y R^{31} son, independientemente, hidrógeno o alquil- R^{25} ;

R^{13} es H;

R^{17} es Br, Cl, o F;

R^{18} es halo o metoxi; y

R^{19} es H.

Los ejemplos adecuados de las sales de los compuestos de acuerdo con la invención incluyen ácidos inorgánicos u orgánicos. Estos incluyen, pero no están limitados a, clorhídrico, bromhídrido, sulfato, metanosulfato, maleato, fumarato, fosfato y otras sales farmacéuticamente aceptables. Las sales que son inadecuadas para usos farmacéuticos pero que se pueden emplear, por ejemplo, para el aislamiento o purificación de compuestos libres de la fórmula I o sus sales farmacéuticamente aceptables, también están incluidas.

125
156

Todos los estereoisómeros de los compuestos de la invención presente se contemplan, bien sea en mezcla o en forma pura o sustancialmente pura. La definición de los compuestos de acuerdo con la invención abarca todos los estereoisómeros posibles y sus mezclas. Esta muy particularmente abarca las formas racémicas y los isómeros ópticos aislados que tienen la actividad especificada. Las formas racémicas se pueden resolver mediante métodos físicos, tales como, por ejemplo, cristalización fraccional, separación o cristalización de los derivados diastereoméricos o separación mediante cromatografía de columna quiral. Los isómeros ópticos individuales se pueden obtener de los racematos mediante métodos convencionales tales como, por ejemplo, formación de sal con un ácido óptimamente activo seguido por cristalización.

Se debe entender que la presente invención incluye formas de prodroga de los compuestos de fórmula I. Varias formas de prodroga son bien conocidas en la Técnica. Para ejemplos de tales derivados de prodroga, ver:

(a) Designo f Prodrugs, edited by H. Bundgaard (Elsevier, 1985); y Methods in Enzimology, Vol. 42, pp. 309-396, editado por K.

B6
157

Widder et al., (Academia Press, 1985);

(b) A Textbook of Drug Design and Development, editado por Krosgaard-Larsen y H. Bundgaard, capítulo 5, "Design and Application of Prodrugs," por H. Bundgaard, pp. 113-191 (1991);

(c) H. Bundgaard Advanced Drug Deliver Reviews, 8, pp. 1-38 (1992);

(d) H. Bundgaard et al., Journal of Pharmaceutical Sciences, 77, 285, (1988);

(e) N. Kayeka et al., Chem. Phar. Bull., 32, 692 (1984).

La invención también suministra una composición farmacéutica que comprende un compuesto de fórmula I, como se definió anteriormente, y un portador farmacéuticamente aceptable y al menos otro agente anticancerígeno formulado como una dosis fija. Los agentes anticancerígenos preferidos se seleccionan del grupo que consiste de: tamoxifen, toremifen, raloxifene, droloxifeno, yodoxifeno, megestrol, acetato, anastrozol, letrozol, borazol, exemestano, flutamida, nilutamida, bicalutamida, acetato de ciproterona, acetato de goserelina, luprolida, finasterida, herceptina, metotrexato, 5-fluoracilo, citosina arabinosida, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicin-C, dactinomicina, mitramicina, cisplatina, carboplatina, melfalan, clorambucil, busulfan,

137
158

ciclofosfamida, ifosfamida, nitrosoureas, tiotefan, vincristina, taxol, taxotere, etoposido, teniposido, amsacrina, irinotecan, topotecan, y epotilona; un inhibidor de tirosina cinasa tal como Iresa o OSI-774; un inhibidor de angiogénesis; un inhibidor de EGF; un inhibidor de VEGF; un inhibidor de CDK; un inhibidor de Her1/2 unos anticuerpos monoclonales dirigidos contra receptores del factor del crecimiento tales como erbitux (EGF) y herceptina (Her2).

La invención además suministra un método de tratamiento para tratar una condición por vía de la modulación de al menos una enzima de tirosina cinasa que comprende administrar a especies de mamíferos necesitados de tal tratamiento una cantidad efectiva de un compuesto de fórmula I, como se definió anteriormente.

Adicionalmente, la invención suministra un método para tratar una condición por vía de modulación de al menos una enzima de tirosina cinasa que comprende administrar a unas especies de mamíferos necesitados de tal tratamiento una cantidad efectiva de un compuesto de fórmula I como se definió anteriormente, en combinación (simultanea o secuencialmente) con al menos u otro agente anticancerígeno.

3/159

Una condición preferida, tratada mediante dichos métodos de la invención precedente, es cáncer. Adicionalmente, la enzima de tirosina cinasa puede incluir (pero no esta limitada a): Abl, CDK, EGF, EMT, FGF, FAK, Flk,-1/KDR, HER-2, IGF-1R, IR, LCK, MET, PDGF, Src, y VEGF.

La invención también suministra un método para tratar cáncer, que comprende administrar a unas especies de mamífero necesitados de tal tratamiento, una cantidad terapéuticamente efectiva de al menos una de las composiciones farmacéuticas definidas anteriormente.

La invención proporciona además un método para tratar enfermedades proliferativas, que comprende administrar a unas especies de mamíferos necesitadas de tal tratamiento una cantidad terapéuticamente efectiva de al menos una de las composiciones farmacéuticas definidas anteriormente.

Ciertos compuestos de fórmula I pueden generalmente ser preparados de acuerdo con los siguientes esquemas y el conocimiento de un experto en la técnica. Solvatos (por ejemplo, hidratos (de los compuestos de fórmula I están también dentro del alcance de la presente invención. Los métodos de solvatación son generalmente

29
160

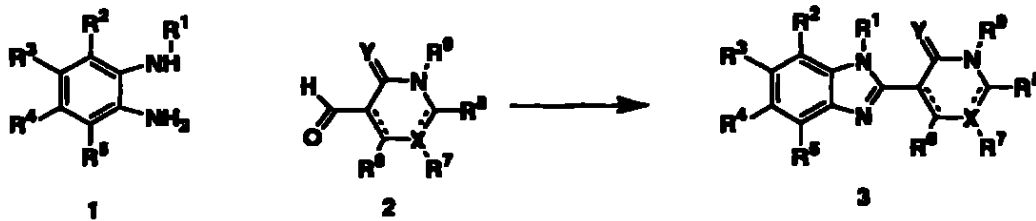
conocidos en la técnica. De acuerdo con esto, los compuestos de la presente invención pueden estar en forma libre o de hidrato, o se pueden obtener mediante métodos ejemplificados por los siguientes esquemas de adelante.

Más específicamente, los esquemas I-VII ilustran la preparación de los compuestos reivindicados en esta invención. Los ejemplos, que siguen ilustran los compuestos que se pueden sintetizar mediante estos esquemas. Los esquemas no están limitados por los ejemplos listados o por ningunos sustituyentes empleados con propósitos ilustrativos.

El esquema I describe la preparación de benzimidazoles. Las diaminas 1 de partida son fácilmente disponibles utilizando métodos de literatura o se obtienen comercialmente. La diamina es entonces condensada con aldehído 2 para suministrar el benzimidazol 3. La modificación adicional de los grupos funcionales del grupo arilo del benzimidazol o heterociclo de 3 son entonces previstas.

140
161

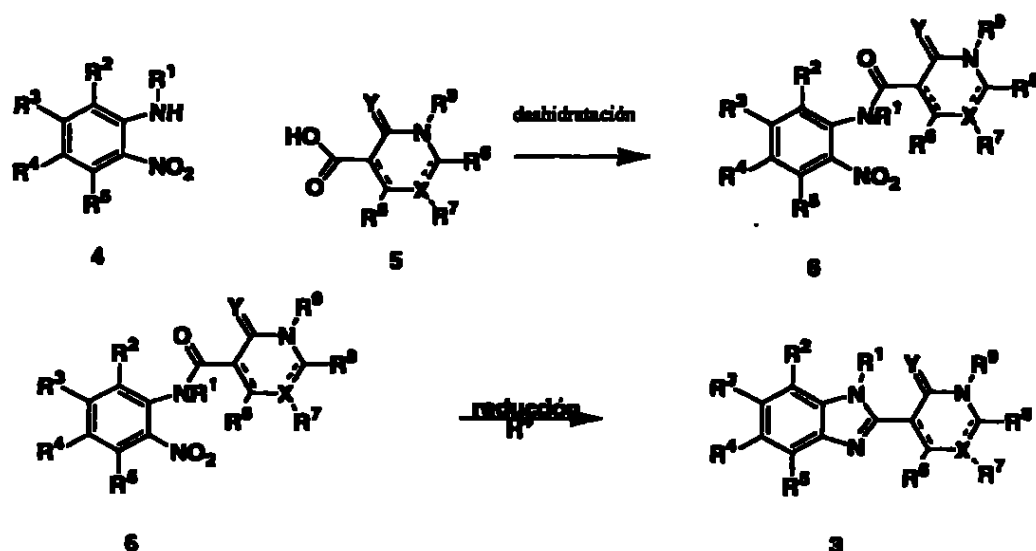
Esquema I



Alternativamente, el benzimidazol se podría formar de una manera en forma de etapa (ver esquema II) mediante formación de amida utilizando el cloruro ácido de 5 o cualquiera de los reactivos acoplantes de péptido comúnmente utilizados tales como DCC (diciclohexilcarbodiimida), clorohidrato de EDCI (1-(3-dimetilaminopropil)-3-etilcarbodiimida), etc. Una vez la amida 6 se forma el grupo nitro se puede reducir utilizando hidrogenación catalítica, hidrogenación de transferencia o reducción química tal como SnCl_2 o polvo de hierro u otros métodos conocidos en la técnica para reducción de grupos aril nitro. El tratamiento de la anilina con ácido formaría entonces el benzimidazol.

~~162~~

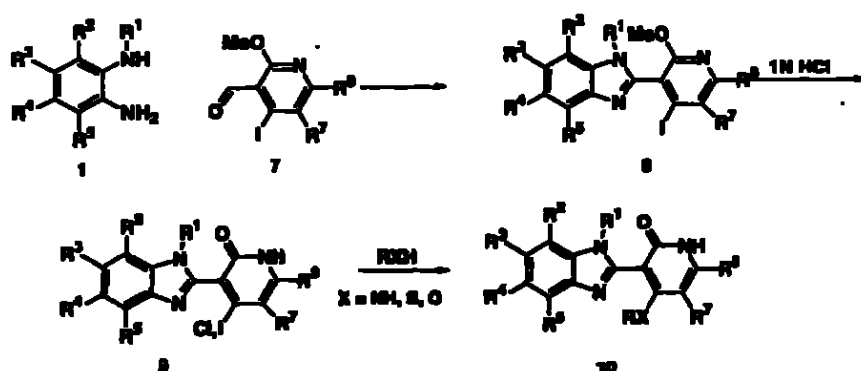
Esquema II



Por ejemplo, el esquema III ilustra el uso de 4-yodo-2-metoxi-piridina-3-carbaldehído 7 para suministrar el benzimidazol funcionarizado 8. La hidrólisis del grupo metoxi utiliza condiciones ácidas próticas, TMSI (trimetilsilil yoduro), BBr_3 , u otras condiciones conocidas en la técnica para dividir un metileter suministraría la halopiridina 9. La adición de nucleófilos de heteroatomo utilizando aminas, alcoholes o tioles suministraría entonces las piridonas sustituidas 10. Otra funcionalidad podría ser incorporado dentro del aldehído y el anterior ejemplo se incluye solamente con propósitos de ilustración.

142
163

Esquema III

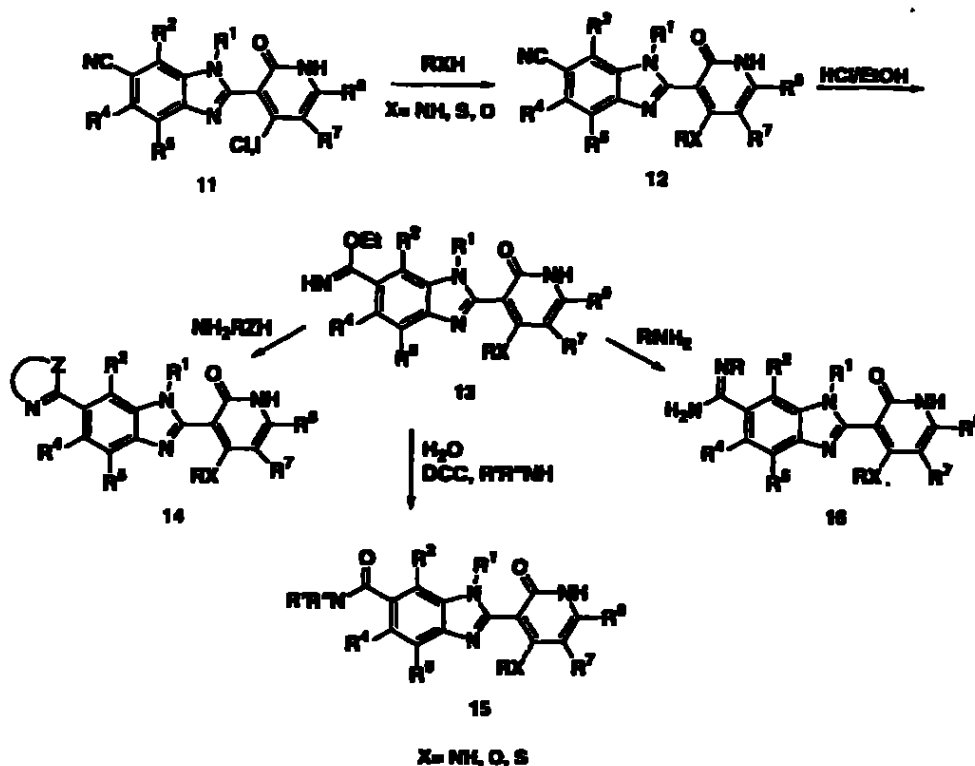


De manera similar el anillo de arilo del benzimidazol preparado utilizando los esquemas I o II se puede modificar. Por ejemplo la introducción de un grupo ciano para R^3 sobre el benzimidazol permite la formación de heterociclos tales como imidazol, imidazolinas, oxazolinas, tiazolinas, amidas, o amidinas. El esquema IV ilustra tales transformaciones. Partiendo del benzimidazol 11 ciano-sustituido el heterociclo se puede modificar como se ilustra en el esquema IV para suministrar 12. La formación de imidato preferiblemente utiliza etanol y ácido suministra el intermedio 13. El imidato 13 se puede transformar utilizando diaminas para formar imidazolinas, amino alcoholes para formar oxazolinas, amino acetales para formar imidazoles, y amino tioles para formar tiazolinas 14. Alternativamente el imidato se puede hidrolizar al ácido y acoplar con

164

aminas utilizando cualquiera de los reactivos de formación de amida estándar (DCC, EDCI, etc.) para formar amidas 15. El imidato 13 también es un intermedio útil para la preparación de amidinas 16 al reaccionar con aminas.

Esquema IV

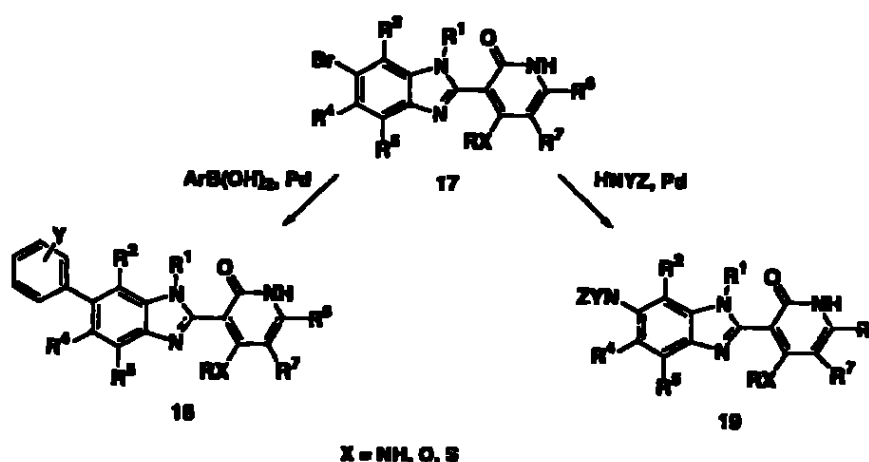


El esquema V ilustra la transformación adicional de benzimidazoles que llevan un átomo de halógeno utilizando catálisis de paladio utilizando condiciones desarrolladas por Suzuki [Yang et al. Acta Chem. Scand. (1993) 221, Suzuki et al. Synth. Común. (1981) 11. 513] o

165

Buchwald/Hartwig [Buchwald et al. J. Am. Soc. (1994) 116: 7901; Hartwig et al. J. Am. Chem. Soc. (1994) 116: 5969; Hartwig. Angew. Chem. Int. Ed. Engl. (1998) 37: 2046] y variaciones de estos métodos. La preparación de un benzimidazol sustituido con bromo 17 podría ser prevista para suministrar un sustrato para acoplamiento Suzuki con arilo, vinilo, y ácidos borónicos heterocíclicos para suministrar benzimidazoles 18. De manera similar, las aminas y los heterocíclicos tales como piperazina o derivados de morfolina 19 se pueden preparar del mismo bromo utilizando aminas bajo condiciones descritas por Buchwald y Hartwig o variaciones de estos.

Esquema V

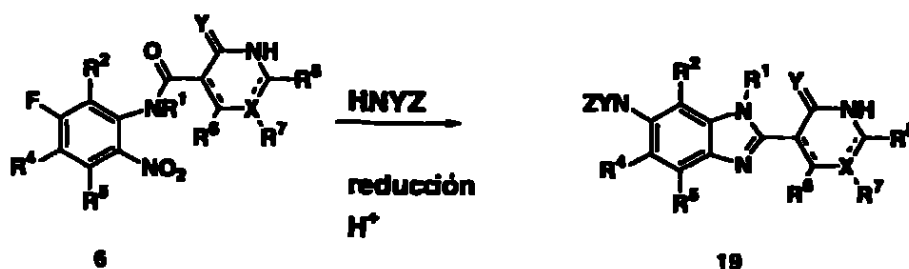


Alternativamente la amina y los derivados heterocíclicos tales como 19 se pueden preparar

145
166

utilizando el intermedio 6 descrito en el esquema II. Cuando el R³ de 6 es un halógeno, preferiblemente F, el halógeno se puede desplazar con aminas, alcoholes, aminas heterocíclicas y otro nitrógeno que contiene heterociclos tales como piperazina, piperidina, 4-amino piperidina, morfolino, imidazol, etc. (esquema VI). El nitrógeno terminal de la piperazina o la 4-amino piperidina pueden entonces ser alquilatados utilizando funciones de alquilación estándar o reaccionar con aldehídos en reacción de animación reductiva para suministrar derivados alquilatados. Alternativamente el átomo de nitrógeno terminal de la piperazina o 4-amino piperidina se pueden acilar o carbamoilatar utilizando cualquier número de condiciones que son de rutina para alguien experto en la técnica de la síntesis orgánica. Siguiendo el ejemplo ilustrado en el esquema II los compuestos tales como 19 se pueden preparar.

Esquema VI



Hf
167

Alternativamente, las aminas, heterociclos y alcoholes se pueden introducir en R³ utilizando una reacción de sustitución aromática nucleofílica que parte de un intermedio 20 donde R³ es halógeno, preferiblemente F, el halógeno se puede desplazar con aminas, alcoholes, aminas heterocíclicas y otro nitrógeno que contiene heterociclos tales como piperazina, piperidina, 4-amino piperidina, morfolino, imidazol, etc. (esquema VII). El nitrógeno terminal de la piperazina o 4-amino piperidina puede entonces ser alquilado utilizando condiciones de alquilación estándar o reaccionar con aldehídos en una reacción de aminación reductiva para suministrar derivados alquilados. Alternativamente el átomo de nitrógeno terminal de la piperazina o 4-amino piperidina se puede acilar o carbamoilatar utilizando cualquier número de condiciones que son de rutina para alguien experto en la técnica de síntesis orgánica. La nitro anilina resultante se puede reducir a diamina 21 y procesar como se ilustra en el esquema II.

~~168~~

Esquema VII



UTILIDAD

Los compuestos de acuerdo con la invención tienen propiedades farmacológicas; en particular, los compuestos de la fórmula I son inhibidores de la enzima tirosina cinasa. Los compuestos novedosos de la fórmula I son así útiles en terapia de una variedad de enfermedades proliferativas (que incluyen pero no están limitadas a enfermedades asociadas con enzimas de tirosina cinasa) tales como cáncer, enfermedades autoinmunes, enfermedades virales, enfermedades fungosas, desordenes neurodegenerativos y enfermedad cardiovascular.

Más específicamente, los compuestos de fórmula I son útiles en el tratamiento de una variedad de cánceres, incluyendo, pero no estando limitados a, lo siguiente:

169

a) carcinoma incluyendo aquella de la vejiga, pecho, colón, riñón, hígado, pulmón, incluyendo cáncer pulmonar de célula pequeña, esófago, vesícula biliar, ovario, páncreas, estómago, cérvix, tiroide, próstata y piel, incluyendo carcinoma celular escamoso;

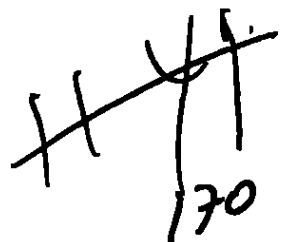
b) tumores ematopoiéticos de linaje linfoide, incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de célula B, Linfoma de célula T, linfoma Hodgkins, linfoma no Hodgkins, linfoma de célula vellosa y linfoma de Burketts:

c) tumores ematopoiéticos de linaje mieloide, incluyendo leucemias mielógenas agudas y crónicas, síndrome mielodisplástico y leucemia promielocítica;

d) tumores de origen mesenquimal, incluyendo fibrosarcoma y rabdomiosarcoma,

e) tumores del sistema nervioso central y periférico, incluyendo astrocitoma, neuroblastoma, glioma, y schwannomas; y

f) otros tumores, incluyendo sarcoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma, y



pigmentoso, keratocantoma, cáncer folicular tiroide y sarcoma kaposi.

Debido al papel clave de las tirosinas cinasas en la regulación de la proliferación celular en general, los inhibidores podrían actuar como agentes citostáticos reversibles que pueden ser útiles en el tratamiento de cualquier proceso y enfermedad que se caracteriza por proliferación anormal celular, por ejemplo, hiperplasia prostática benigna, por poliposis adenomatosis familiar, neuro-fibromatosis, aterosclerosis, fibrosis pulmonar, artritis, soriasis, glomerulonefritis, restenoides que sigue a la angioplastia o cirugía vascular, formación de cicatriz hipertrófica, enfermedad inflamatoria del intestino rechazo de transplante, ataque endotóxico, e infección fungosa.

Los compuestos de fórmula I pueden inducir apoptosis. La respuesta apoptótica es aberrante en una variedad de enfermedades humanas. Los compuestos de fórmula I, como modulares de la apoptosis, serán útiles en el tratamiento del cáncer (incluyendo pero no estando limitados a aquellos tipos mencionados aquí anteriormente), infecciones virales (incluyendo pero no estando limitadas a herpes virus, pox virus, virus Epstein-Barr, virus Sindbis y adenovirus), prevención de

15/10
171

desarrollo de SIDA en individuos infectados con HIV, enfermedades auto inmunes (incluyendo pero no estando limitadas a lupus sistémico, eritematoso, glomerulonefritis mediada auto inmune, artritis reumatoide, soriasis, enfermedad inflamatoria del intestino, y diabetes mielitus autoinmune), desordenes neurodegenerativos (incluyendo pero no limitados a enfermedad de Alzheimer, demencia relacionada con SIDA, enfermedad de parkinson, esclerosis lateral amiotrófica, retinitis pigmentosa, atrofia muscular espinal y degeneración cerebral), síndromes mielodisplásticos, anemia aplástica daño isquémico asociado con infartos del miocardio, ataques y daño de reperfusión, arritmia, arteriosclerosis, enfermedades del hígado relacionadas por alcohol o inducidas por tóxina, enfermedades hematológicas (incluyendo pero no estando limitadas a anemia crónica y anemia aplástica), enfermedades degenerativas del sistema musculoesqueletal (incluyendo pero no estando limitadas a osteoporosis y artritis) rinosinusitis sensible a la aspirina, fibrosis sistica, esclerosis múltiple, enfermedades del riñón y dolor de cáncer.

Los compuestos de fórmula I pueden modular el nivel de síntesis de ARN y ADN celular. Estos agentes serían por lo tanto útiles en el tratamiento de infecciones

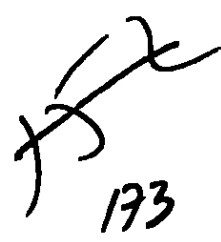
151
172

virales (que incluyen pero no están limitadas a HIV, virus de papiloma humano, herpes virus, poxvirus, virus Epstein-Barr, virus Sindbis y adenovirus).

Los compuestos de fórmula I pueden también ser útiles en la quimio prevención del cáncer. La quimio prevención se define como la inhibición del desarrollo de cáncer imbasivo mediante el bloqueo del evento mutagénico iniciante o por el bloqueo de la progresión de células pre malignas que ya han sufrido un insulto o recaída de inhibición de tumor.

Los compuestos de fórmula I también pueden ser útiles para inhibir la angiogénesis y la metástasis tumoral.

Los compuestos de esta invención también pueden ser útiles en combinación (administrados juntos o secuencialmente) con tratamientos anti cancerígenos conocidos tales como terapia de radiación o con agentes citostáticos o citotóxicos tales como, por ejemplo, pero no limitados a, agentes interactivos de ADN tales como ciplastina o doxorubicina, inhibidores de topoisomerasa II, tales como etoposido; inhibidores de topoisomerasa I tales como CPT-11 o topotecán; agentes interactuantes de tubulina, tales como paclitaxel, docetaxel, o las



epotilonas, agentes hormonales, tales como tamoxifen; inhibidores de timidilato cintaza tales como 5-fluoroacilo, y anti-metabolitos, tales como metotrexato; inhibidores de tirosina cinasa tales como Iresa y OSI-774; inhibidores de angiogenesis; inhibidores de EGF; inhibidores de VEGF; inhibidores de CDK; inhibidores de Her1/2 y anticuerpos monoclonales dirigidos contra receptores de factor del crecimiento tales como erbitux (EGF) y herceptina (Her2).

Si se formula como una dosis fija, tal combinación de productos emplea los compuestos de esta invención dentro del rango de dosis descrito adelante y el otro agente farmacéuticamente activo o tratamiento dentro de su tratamiento de rango de dosis aprobado. Los compuestos de fórmula I también se pueden administrar secuencialmente con agentes anticancerígenos o citotóxicos conocidos cuando una formulación de combinación es inapropiada. La invención no está limitada a la secuencia de administración; los compuestos de fórmula I se pueden administrar bien sea antes o después de la administración de los agentes anticancerígenos o citotóxicos conocidos.

La materia objeto adicional de la invención también incluye farmacéuticos para uso, como se describió

1253
174

anteriormente, incluyendo control de cáncer, inflamación y artritis, que contiene al menos un compuesto de fórmula I como se definió anteriormente o al menos una de sus sales de adición ácida farmacéuticamente aceptables, y el uso de un compuesto de la fórmula I como se definió anteriormente para la preparación de un fármaco que tiene actividad contra enfermedades proliferativas como se describió previamente incluyendo contra cáncer, inflamación y/o artritis.

Las propiedades farmacológicas de los compuestos de esta invención se pueden confirmar mediante un número de ensayos farmacológicos. Los ensayos farmacológicos ejemplificados que siguen se han llevado a cabo con los compuestos de acuerdo con la invención y sus sales.

Ensayos biológicos

A. Ensayo de CDK 2/ciclina E cinasa

Las reacciones de cinasa consistieron de 5 ng de complejo GST-CDK 2/ciclina E expresado en baculovirus, 0,5 µg de proteína de fusión GST-RB (aminoácidos 776-928 e proteína retinoblastoma), 0,2 µCi ³³Pγ-ATP, 25 µM ATP en 50 µl de amortiguador de cinasa (50 mM Hepes, pH 8,0, 10 mM de MgCl₂, un mM de EGTA, 2 mM de DTT). Las reacciones



se incubaron durante 45 minutos a 30°C y se pararon mediante la adición de ácido tricloroacético frío (TCA) a una concentración final del 15%. Los precipitados PCA se recolectaron sobre platos unifiltro GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal Filtermate (Packard Instrument Co., Meriden, CT) y los filtros se cuantificaron utilizando un contador de centelleo líquido de 96 pozos counter (Packard Instrument Co, Meriden, CT). Las curvas de respuesta de dosis fueron generadas para determinar la concentración requerida que inhibe el 50% de la actividad de cinasa (IC_{50}). Los compuestos fueron disueltos a 10 mM en dimetilsulfóxido (DMSO) y se evaluaron en 6 concentraciones cada uno en triplicado. Las concentraciones finales de DMSO en el ensayo igualaron el 2%. Los valores IC_{50} se derivaron mediante análisis de regresión no lineal y tenían un coeficiente de varianza ($SD/medio, n=6$) = 145.

B. Ensayo de Cinasa EMT

Un ensayo de cinasa basado en filtro, mide la fosforilación de Gst-SLP76 mediante Gst-Emtk, se empleo para determinar la actividad inhibitoria del compuesto contra Emt. La reacción de cinasa se desarrollo en un plato de 96 pozos a temperatura ambiente durante 15

176

minutos antes de ser terminad agregar 100 μ l de ácido tricloroacético, al 20% (TCA) que contiene pirofosfato de sodio 0,1 M. La mezcla de reacción de quinaza (60 μ l) contenía 25 mM HEPES, pH 7,0 0,1 mg/ml BSA, 5 mM MgCl_2 , 5 mM MnCl_2 , 8 ng de enzima (Gst-Emtk), 5 μ g de proteína de sustrato (Gst-SLP76), 1 μ M de ATP, 0,4 μ Ci de $[\gamma\text{-P}^{33}]\text{ATP}$ y el compuesto ensayado (en concentraciones varias). Después de la terminación, a las proteínas se les permitió precipitarse en la presencia de TCA durante 1 h a 4°C. Las proteínas precipitadas fueron entonces cosechadas sobre un plato de filtro (unifilter-96, GF/C, Packard Instrument) y lavada para remover el exceso $[\gamma\text{-P}^{31}]\text{ATP}$. La radioactividad se determinó utilizando un TopCount NXT (Packard Instrument) después de agregar 35 μ l de Microscint 20 (Packard Instrument).

C. Ensayo FAK de tirosina cinasa

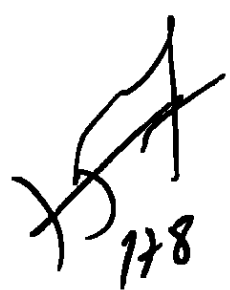
La adhesión focal de la cinasa se analizó utilizando el polímero sintético poli(Glu/Tyr) (SigmaChemicals) como un sustrato fosfoceptor. Cada mezcla de reacción consistió de un volumen total de 50 μ l y contenía 100 ng de enzima expresada en baculovirus, 2 μ g de poli(Glu/Tyr), 1 μ M de ATP, y 0,2 μ Ci de $[\gamma\text{-}^{33}\text{P}]\text{ATP}$. Las mezclas también contenían 40 mM de Tris, HCl, pH 7,4, 1 mM MnCl_2 , 0,5 mM DTT, y 0,1 mg/ml de albumina de suero

156
177

Bovina. Las mezclas de reacción se incubaron a 26°C durante 1 hora y la actividad de la cinasa se determinó mediante cuantificación de la cantidad de fosfato radioactivo transferido al sustrato de poli(Glu/Tyr). La incorporación se midió mediante la adición de ácido tricloracético frío (TCA) la precipitación de las proteínas que se recolectó sobre platos unifiltros GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal Filtermate y los filtros fueron cuantificados utilizando un contador de centelleo líquido de 96 pozos TopCount (Packard Instrument Co., Meriden, Ct). Los compuestos se disolvieron en dimetil sulfóxido a una concentración de 10 mM y se evaluaron a seis concentraciones, cada una en triplicado. La concentración final de DMSO agregado al ensayo de cinasa fue de 0,55%, el cual había mostrado no tener efecto sobre la actividad de la cinasa. Los valores IC50 fueron derivados por análisis de regresión no lineal y tienen un coeficiente de varianza (SD/medio, n = 6) = 16%.

D. Ensayo De cinasa HER-1/HER-2

Las reacciones de cinasa consistieron de 10 ng GST-HER1, expresados en baculoviros, 100 ng de HER2, 100 ng/ml de poli(Glu/Tyr) (Sigma) 0,2 µCi 33p γ-ATP, 1 µM ATP en 50 µl de un amortiguador de cinasa (50 mM de Tris,



pH 7,5, 10 mM de MnCl_2 , 0,5 mM de DTT). Las reacciones se incubaron durante 1 hora a 27°C y se pararon durante la adición de ácido tricloroacético frío (TCA) para una concentración final del 15%. Los precipitados TCA se recolectaron sobre platos unifiltros GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal filtermate (Packard Instrument Co., Meriden, CT) y los filtros se cuantificaron utilizando un contador de centellón líquido de 96 pozos TopCount (Packard Instruments Co., Meriden, CT). Las curvas de respuesta de dosis se generaron para determinar la concentración requerida para inhibir el 50% de la actividad de cinasa (IC_{50}). Los compuestos se disolvieron a 10 mM en dimetilsulfoxido (DMSO) y se evaluaron en seis concentraciones, cada una en triplicado. La concentración final DMSO en el ensayo igualó el 1%. Los valores IC_{50} se derivaron mediante análisis de regresión no lineal y tienen un coeficiente de varianza (SD/medio , $n = 6$) = 16%.

E. Ensayo de Tirosina Cinasa de Receptor IGF

La tirosina cinasa de receptor IGF-1 se ensayó utilizando el polímero sintético poli(Glu/Tyr) (Sigma Chemicals) como un sustrato fosfoaceptor. Cada mezcla de reacción consistió de un volumen total de 50 μl y

158
179

contenía 125 ng de enzima expresada en baculovirus, 2,5 µg de poli(Glu/Tyr), 25 µM de ATP, y 0,1 µCi de $[\gamma\text{-}^{33}\text{P}]$ ATP. La mezcla también contenía 20 mM de MOPS, Ph 7,0, 5 mM MnCl_2 , 0,5 mM de DDT, y 0,1 mg/ml de albúmina de suero bovino. Las mezclas de reacción se incubaron a 30°C durante 45 minutos y la actividad de cinasa se determinó mediante cuantificación de la cantidad de fosfato radiactivo transferido al sustrato de poli(GluTyr). La incorporación se midió mediante la adición de precipitación de ácido tricloracético frío (TCA) de las proteínas que fueron recolectadas sobre los platos unifiltro GF/C (Packard Instruments Co., Meriden, CT) utilizando un cosechador universal Filtermate y los filtros se cuantificaron utilizando un contador de centelleo líquido de 96 pozos TopCount (Packard Instrument Co., Meriden, CT). Los compuestos se disolvieron en dimetil sulfoxido a una concentración de 10 mM y se evaluaron a seis concentraciones, cada una en triplicado. Las concentraciones finales en DMSO agregado a los ensayos de cinasa fue de 0,5%, el cual había mostrado no tener efectos sobre la actividad de cinasa. Los valores IC_{50} se derivaron mediante análisis de regresión no lineal y tienen un coeficiente de varianza (SD/medio, $n = 6$) = 16%.



F. Ensayo de Tirosina Cinasa de Receptor de Insulina

La tirosina cinasa de receptor de insulina se ensayó utilizando el polímetro sintético poli(Glu/Tyr) (Sigma Chemicals) como un sustrato fosfoaceptor. Cada mezcla de reacción consistió de un volumen total de 50 μ l y contenían 90 ng de enzima expresada en baculovirus, 2,5 μ g de poli(Glu/Tyr), 25 μ M de ATP, y 0,1 μ Ci de [γ - ^{33} P]ATP. Las mezclas también contenían 20 mM de Tris. HCL, Ph 7,4, 5 mM de mM MnCl_2 , 0,5 mM de DDT, y 0,1 mg/ml de suero bovino. La mezcla de reacción se incubó a 26°C durante 1 hora la actividad de cinasa se determinó mediante cuantificación de la cantidad de fosfato radiactivo transferido al sustrato de poli(Glu/Try). La incorporación se midió mediante la adición de precipitación de ácido tricloracético frío (TCA) de las proteínas que se recolectaron sobre los platos unifiltro GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal Filtermate y los filtros se cuantificaron utilizando un contador de centelleo líquido de 96 pozos TopCount (Packard Instrument Co., Meriden, CT). Los compuestos se disolvieron en dimetilsulfoxido a una concentración de 10 mM y se evaluaron a seis concentraciones, cada una en triplicado. La concentración final del DMSO agregada a los ensayos de cinasa fue del 0,5%, lo cual había mostrado no tener efecto sobre la

160
181

actividad de cinasa. Los valores IC₅₀ se derivaron mediante análisis de regresión no lineal y tienen un coeficiente de varianza (SD/medio, n = 6 = 16%.

G. Ensayo de Cinasa LCK.

Las reacciones de cinasa consistieron de 10 ng de Baculovirus expresado 10 ng GST-Lck, 100 ng/ml poli(Glu/Tyr) (Sigma), 0, μ Ci ³³p γ -ATP, 1 μ M ATP en 50 μ l de amortiguador de cinasa (50 mM, Tris, Ph 7,5, 10 mM de mM MnCl₂, 0,5 mM de DDT). La reacción se incubó durante 1 h a 27°C y se pararon mediante la adición de ácido tricloroacético frío (TCA) a una concentración final del 15%. Los precipitados TCA se recolectaron sobre platos unifiltro GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal Filtermate (Packard Instrument Co., Meriden, CT) y los filtros se cuantificaron utilizando un contador de centelleo líquido de 96 pozos TopCount (Packard Instrument Co., Meriden, CT). Las curvas de respuesta de dosis generadas para determinar las concentraciones requirieron inhibir el 50% de la actividad de cinasa (IC₅₀). Los compuestos se disolvieron en 10 mM de dimetilsulfóxido (DMSO) y se evaluaron en seis concentraciones, cada una en triplicado. La concentración final de DMSO en el ensayo igualaron e 1%. Los valores

f6t
182

IC₅₀ se derivaron mediante análisis de regresión no lineal y tienen un coeficiente de varianza (SD/medio, n = 6 = 16%.

H. Ensayo de Cinasa MET.

Las reacciones de cinasa consistieron de 10 ng de baculovirus expresados GST-Met, 2,5 ug poli(Glu/Tyr) (Sigma) 0,2 µCi 33p γ-ATP, 10 µM ATP en 50 µl de un amortiguador de cinasa (40 mM Tris, pH 7,5, 1 mM de MnCl₂, 0,5 mM de DTT). Las reacciones se incubaron durante 1 hora a 27°C y se pararon durante la adición de ácido tricloroacético frío (TCA) para una concentración final del 3,5%. Los precipitados TCA se recolectaron sobre platos unifiltros GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal filtermate (Packard Instrument Co., Meriden, CT) y los filtros se cuantificaron utilizando un contador de centellón líquido de 96 pozos TopCount (Packard Instruments Co., Meriden, CT). Las curvas de respuesta de dosis se generaron para determinar la concentración requerida para inhibir el 50% de la actividad de cinasa (IC₅₀). Los compuestos se disolvieron a 10 mM en dimetilsulfoxido (DMSO) y se evaluaron en siete concentraciones, cada una en triplicado. La concentración final DMSO en el ensayo igualó el 1%. Los valores IC₅₀ se

162
183

derivaron mediante análisis de regresión no lineal y tienen un coeficiente de varianza (SD/medio, $n = 6$) = 16%.

I. Ensayo de Cinasa Receptor PDGF

Las reacciones de cinasa consistieron de 70 ng de baculovirus expresado GST-PDGFR, 0,3 ug de poliGlu/Tyr biotinilado (Sigma), En 50 μ l de amortiguador de cinasa (20 mM HEPES, pH 7,5, 0,7 μ M ATP, 10 mM de $MnCl_2$, 0,5 mM de DTT), 0,15 mM NaCl 0, 1 mg/ml de BSA). Las reacciones se incubaron durante 30 minutos a temperatura ambiente con agitación y detención mediante la adición de 10 μ l de 0,2 M de EDTA pH8,0. 150 μ l de amortiguador de detección HTRF se agregó y se incubó durante 1 hora y 30 minutos a temperatura ambiente. Los conteos fueron cuantificados sobre un HTRF Discovery Packard Instrument.

J. Ensayo de Cinasa VEGFR-2 (KDR)

Las reacciones de cinasa consistieron de 7,5 ng de baculovirus expresado GST-KDR, 1,5 ug de poli(Glu/Tyr) (Sigma), 0,0042 μ Ci 33p γ -ATP, 2,5 mM ATP en 50 μ l de un amortiguador de cinasa (25 mM de Tris, pH 7,5, 1,8 mM de $MnCl_2$, 0,0,625 mM de DTT). Las reacciones se incubaron durante 1 hora a 27°C y se pararon durante la adición de

16
184

ácido tricloroacético frío (TCA) para una concentración final del 15%. Los precipitados TCA se recolectaron sobre platos unifiltros GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal filtermate (Packard Instrument Co., Meriden, CT) y los filtros se cuantificaron utilizando un contador de centellón líquido de 96 pozos TopCount (Packard Instruments Co., Meriden, CT). Las curvas de respuesta de dosis se generaron para determinar la concentración requerida para inhibir el 50% de la actividad de cinasa (IC_{50}). Los compuestos se disolvieron a 10 mM en dimetilsulfoxido (DMSO) y se evaluaron en seis concentraciones, cada una en triplicado. La concentración final DMSO en el ensayo igualó el 1%. Los valores IC_{50} se derivaron mediante análisis de regresión no lineal y tienen un coeficiente de varianza ($SD/medio$, $n = 6$) = 16%.

K. Ensayo de Citotoxicidad (HT-29-colon, Colo 205, MCF-7-breast)

Las líneas celulares de tumor se mantuvieron en un medio McCoy 5A (GIBCO) y suero bovino fetal inactivado con calor al 10% (GIBCO). La citotoxicidad in vitro es estimada en las células tumorales mediante un ensayo colorimétrico basado en tetrazolium que toma ventaja de la conversión metabólica de MTS (3-(4,5-dimetiltiazol-2-

16/185

11)-5-(3-carboximetoxifenil)-2-(4-sulfenil)-2H-tetrazolium, sal inerte) (Promega) a una forma reducida que absorbe luz a 492 nm (1). Las células son sembradas 24 horas antes para adición de droga. Luego de una incubación de 72 horas a 37°C con un compuesto de ensayo diluido serialmente, MTS (Riss, T.L. et al., Comparison of MTT, XTT, and a novel tetrazolium compound MTS for in vitro proliferation and chemosensitivity assays," Mol. Biol. Cell. 3 (suppl.): 184a 1992), en combinación con el agente acoplante de electrones fenazina metosulfato, se agrega a las células. La incubación se continua durante 3 horas, luego la absorbancia del medio a 492 nm se mide con un espectrofotómetro para obtener el número de células sobrevivientes con relación a las poblaciones de control. Los resultados son expresados como concentraciones citotóxicas medias (valores IC₅₀).

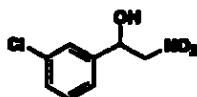
Tabla 1 - Actividad Biológica (uM); todos los compuestos de la tabla tuvieron actividad de cinasa de <25uM contra uno o más de los siguientes cinasas CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF, HT,-29 y colon -205 son líneas de células de tumores de colon humano y MCF-7 es una línea de células de tumor de pecho humano.

105
186

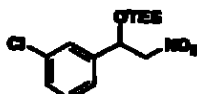
Ejemplo	HT-29	MCF-7	Colo205
1	1,0		
3	2,0		
399	0,4		0,8
400	0,8		0,9
411	0,7		0,9
517	0,3		
519	0,3	0,6	
520	0,6	0,2	
521	0,5		
522	0,7	0,1	0,1
523	0,6		
524	0,6		
525	1,1		
526	1,4		
527	1,3	0,1	0,3
534	0,4		
538	0,9		
544	0,3	0,6	
553	0,9	0,3	0,2
554	0,7	0,2	0,3
555	0,2	0,1	0,2
559	0,6	0,3	
574	0,2		
581	0,2	0,3	
582	0,1	0,2	
583	0,1	0,2	
584	0,3	0,2	
585	0,7	0,3	
590	0,8	0,2	0,2
593	0,7		

166
187

Procedimiento General para la preparación de 2-hidroxi-2-
(fenilsustituido)-etilaminas:



1-(3-cloro-fenil)-2-nitro-etanol: A una solución de 3 -cloro-benzaldehído (20 g, 0,142 mol) en nitrómetano (100 ml) se agregó sulfato de magnesio (37,6 g, 0,312 mol) y base de fosfazeno P₁-t-bu-tris(tetrametileno) (4,43G, 0,014 mol). La mezcla d reacción se agitó a temperatura ambiente durante 2 h. Después de concentración in vacuo, el residuo se purificó mediante cromatografía de destello (25% EtOAc/hexano) para producir el compuesto del título (26,4 g, 100%) como un aceite amarillo verdoso. ¹H NMR (300 MHz, DMS-d₆) δ 7,53 (1H), s), 7,35-7,42 (3H, m), 6,23 (1H, broad s), 5,32-5,33 (1H, m) 4,90 (1H, dd, J = 3,2, 12, 4 Hz), 4,60 (1H, dd, J = 1,2, 12, 4 Hz).

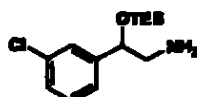


[1-cloro-fenil)-2-nitro-etoxi]-trietyl-silano: A una solución de 1-(3-cloro-fenil)-2-nitro-etano (26 g 0,14

167
188

mol) en DMF ((50 ml se agregó imidazol (28, 6 g, 0,42 mol) y clorotrietilsilano (25, 3 g, 0,17 mol). La mezcla de reacción se agitó temperatura ambiente durante 2 h. Después se apagó con agua, la mezcla se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y agua salobre, se secaron sobre Na₂SO₄ y se filtraron. Después de la remoción del solvente, el producto crudo se purificó mediante cromatografía de destello (2% EtOAc/hexano) para producir el compuesto del título (37 g, 91%) como aceite incoloro.

¹H NMR (300 MHz, CDCl₃) δ 7.40 (1H, s), 7.27 – 7.32 (3H, m), 5.40 (1H, dd, *J* = 3.2, 9.5 Hz), 4.51 (1H, dd, *J* = 9.5, 12.1 Hz), 4.36 (1H, dd, *J* = 3.3, 12.1 Hz), 0.85 (9H, t, *J* = 7.5 Hz), 0.54 (6H, q, *J* = 7.5 Hz).



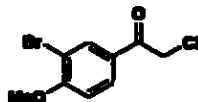
2-(3-cloro-fenil)-2-trietilsilaniloxi-etilamina: Nickel Raney (1 g) se lavó con agua destilada 5 veces y metanol 3 veces. [1-(3-cloro-fenil)-2-nitro-etoxi]-trietil-silano (10 g, 0,032 mol) y nickel Raney en metanol (100 ml) se hidrogeno (35 psi) a temperatura ambiente durante 14 h. La mezcla de reacción se filtró a través de una almohadilla de selita y se enjuagó con metanol. La concentración del filtrado hasta sequedad dio el compuesto del título (5, 6 G, 62%) como un aceite

162
189

incolore el cual se utilizó para la siguiente etapa sin purificación.

¹H NMR (300 MHz, CDCl₃) δ 7.32 (1H, s), 7.18-7.26 (3H, m), 4.70 (1H, t, *J* = 5.8 Hz), 2.86 (2H, m), 0.89 (9H, t, *J* = 7.9 Hz), 0.56 (6H, q, *J* = 7.8 Hz). LRMS (M+H)⁺ *m/z* 286.

Procedimiento general para preparación de 2-hidroxi-2-(fenil sustituido)-etilaminas:

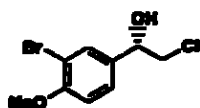


4-metoxi-3-bromofenil cloroacetofenona: A una suspensión de AlCl₃ (13, 4 g, 0,10 mol) en cloruro de metileno (40 ml) se agrega una solución de 2-bromoanisol (12, 5 ml, 0,10 mol) y cloruro de cloroacetilo 8 ml, 0,10 mol) a 0°C. La solución se calentó a temperatura ambiente durante 2 horas y se vertió en hielo y se extrajo con cloruro de metileno, se lavó con solución de bicarbonato de sodio saturado, con agua salobre, y se secó sobre MgSO₄. La solución se filtró, se concentró y se cristalizó de EtOH para dar 15,37 g del sólido blanco. LRMS [M-H]⁻ 260,8; IR/(KBr) 1967, 1048, 1255 cm⁻¹;

169
190

^1H NMR (300MHz, CDCl_3) δ 8.18 (s, 1H), 7.94 (dd, J = 8.67 Hz, 1H), 6.96 (d, J = 8.67 Hz, 1H), 4.62 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (CDCl_3 , 75.5 Hz) δ 188.8, 160.3, 134.1, 129.9, 128.2, 112.4, 111.3, 56.6, 45.3.

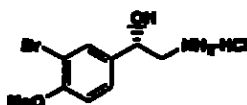
Procedimiento General para la reducción quiral de clorocetonas y amonolisis:



(S)-1-[4-metoxi-3-bromofenil]-2-cloro etanol: A una solución de (S)-metil-CBS-oxazaborolidina (1M) en tolueno, 0,745 ml, 0,745 mmol) y BH_3 -THF (8 ml, 8 mmol) se agregó al mismo tiempo una solución de BH_3 -THF (19 ml, 19 mmol) y una solución de clorocetona (10,03 g, 37,98 mmol) 19 ml de THF. Ambas soluciones se agregaron gota a gota durante 30 minutos. La solución se agitó durante 1 hora y se apagó con adición lenta de metanol (50 ml). La solución se concentró y el residuo se cromatografió sobre una columna corta de sílica gel (1:1 hexano/etil acetato) para dar un rendimiento cuantitativo (10,0 g) de clorohidrina como un aceite claro. IR (KBr) 1053, 1258, 3406 cm^{-1} ;

120
191

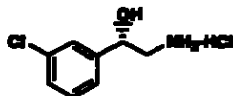
^1H NMR (300MHz, CDCl_3) δ 7.59 (s, 1H), 7.30 (dd, $J=2.16$ Hz, 1H), 6.90 (d, $J=8.46$ Hz, 1H), 4.83 (dd, $J=3.57$ Hz, 1H), 3.90 (s, 3H), 3.64 (ddd, $J=3.6, 11.1, 8.7, 2\text{H}$), 2.04 (b s, 1H). ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 155.9, 133.5, 131.1, 126.3, 111.9, 73.1, 60.4, 56.3, 50.7.



Clorhidrato de (S)-2-amino-1-[3-cloro-4-metoxifenil] etanol: A una solución de la clorohidrina (10,0 g, 37,9 mmol) en 120 ml, de metanol a -40°C se agregaron 100 gramos de amonio. La solución se selló en una botella a presión y se calentó a temperatura ambiente y se agitó durante 48 horas. La solución se enfrió y se abrió. El amonio se le permitió evaporarse y la solución se concentró. El residuo se cristalizó de etanol/acetato de etilo para dar 3,83 g de sólido blanco (35%). El material reaccionó con Boc_2O en acetato de etilo y carbonato de sodio saturado y se analizó mediante HPLC quiral utilizando una columna quiralcel OJ utilizando 95% de hexano/etanol como eluente y se determinó mediante 98% ee. Se recolectaron cultivos adicionales -2,96 g y 1,41 g para un total de 75% de rendimiento.

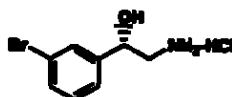
~~12~~
192

LRMS [M+H]⁺ 246; IR (cm⁻¹, KBr) 1055, 1261, 3001, 2948, 3356; ¹H NMR (500MHz, DMSO) δ 8.09 (b s, 2 H), 7.58 (s, 1H), 7.36 (dd, J=2.05, 6.45 Hz, 1H), 7.11 (d, J=8.5 Hz, 1H) 6.10 (s, 1H), 4.80 (m, 1H), 3.84 (s, 3H), 3.00 (ddd, J= 2.7, 12.6, 9.5 Hz, 2H); ¹³C NMR (DMSO, 75.5 MHz) δ 154.8, 135.4, 130.4, 126.6, 112.4, 110.4, 67.9, 56.2, 45.4.



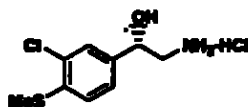
Clorhidrato de (S) 2-amino-2-[3-clorofenil] etanol:
Se preparó de acuerdo con el procedimiento general subrayado anteriormente.

LRMS [M+H]⁺ 172; IR (KBr, cm⁻¹) 3048, 3351, 2952; ¹H NMR (300MHz, MeOD) δ 7.48 (s, 1H), 7.35 (m, 3H), 3.31 (ddd, J= 1.5, 3.12, 9.15 Hz 2H).



Clorhidrato de (S) 2-amino-1-[3-bromofenil] etanol:
se preparó de acuerdo con el procedimiento general subrayado anteriormente.

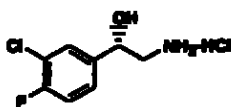
LRMS [MH]⁺ 217.9; IR (KBr, cm⁻¹) 3025, 3443, 2891; ¹H NMR (500MHz, DMSO) δ 7.93 (b s, 2H), 7.60 (s, 1H), 7.52 (d, 1H), 7.41 (s, 1H), 7.35 (d, J=7.7 Hz, 1H) 6.17 (s, 1H), 4.82 (m, 1H), 3.08 (ddd, J= 2.6, 12.7, 9.6 Hz, 2H); ¹³C NMR (DMSO, 75.5 MHz) δ 144.4, 130.5, 128.7, 125.0, 121.6, 68.3, 45.1.

172
193

Clorhidrato de (S)-2-amino-1-[3-cloro-4-metiltiofenil] etanol: se preparó de acuerdo con el procedimiento general subrayado anteriormente.

LRMS [M+H]⁺ 217.9;

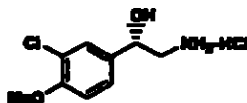
IR (KBr, cm⁻¹) 3007, 3358; ¹H NMR (500MHz, DMSO) δ 8.12 (b s, 2H), 7.46 (s, 1H), 7.37 (s, 1H), 7.35 (d, 1H) 6.19 (d, 1H), 4.83 (m, 1H), 3.01 (ddd, J= 3.2, 12.8, 9.3 Hz, 2H); ¹³C NMR (DMSO, 75.5 MHz) δ 139.6, 136.5, 129.8, 126.6, 125.4, 68.0, 45.2, 14.2.



Clorhidrato de (S)-2-amino-1-[3-cloro-4-fluorofenil] etanol: se preparó de acuerdo con el procedimiento general subrayado anteriormente.

LRMS [M+H]⁺ 189.9; IR (KBr,

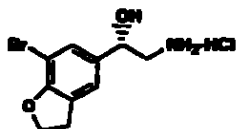
cm⁻¹) 1509, 3008, 3359; ¹H NMR (500MHz, DMSO) δ 8.21 (b s, 2H), 7.61 (d, J=7.85 Hz, 1H), 7.42 (m, 2H), 6.29 (s, 1H), 4.88 (m, 1H), 3.03 (ddd, J= 3.4, 12.8, 9.2 Hz, 2H); ¹³C NMR (DMSO, 75.5 MHz) δ 157.5, 155.5, 139.7, 128.1, 126.7, 119.3, 116.7, 109.0, 67.8, 45.2.



173
194

Clorhidrato de (S)-2-amino-1-[3-cloro-4-metoxifenil]
etanol: se preparó de acuerdo con el procedimiento
general subrayado anteriormente.

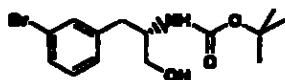
LRMS [M+H]⁺ 202; IR (KBr, cm⁻¹) 3354, 3003, 2949, 1288, 1064; ¹H NMR (500MHz, DMSO) δ 8.18 (brs, 3H), 7.43 (d, J=2.0Hz, 1H), 7.31 (dd, J=8.5, 2.0Hz, 1H), 7.14 (d, J=5.1Hz, 1H), 6.11 (s, 1H), 4.81 (m, 1H), 3.84 (s, 3H), 2.99 (dd, J=13, 3.5Hz, 1H), 2.83 (dd, J=12.5, 9Hz, 1H); ¹³C NMR (DMSO, 125MHz) δ 153.9, 135.0, 127.3, 125.8, 120.8, 112.6, 68.0, 56.1, 45.5; Análisis Elemental Calculado para C₉H₁₂ClNO₂·HCl: C, 45.39; H, 5.50; N, 5.88. Enc.: C, 45.38; H, 5.43; N, 5.70.



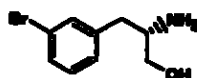
Clorhidrato de (S)-2-amino-1-(7-bromo-2,3-dihidrobenzofurano-5-il)-2-aminoetanol: se preparó de acuerdo con el procedimiento general subrayado anteriormente.

LRMS [M+H]⁺ 258; IR (KBr, cm⁻¹) 3349, 3006, 2928, 1485, 1045, 983; ¹H NMR (500MHz, DMSO) δ 8.13 (brs, 3H), 7.29 (s, 1H), 7.23 (s, 1H), 6.08 (d, J=4 Hz, 1H), 4.76 (m, 1H), 4.61 (t, J=9Hz, 2H), 3.29 (t, J=9Hz, 2H), 2.96 (dd, J=13, 3.5Hz, 1H), 2.82 (dd, J=13.9.5Hz, 1H); ¹³C NMR (DMSO, 125MHz) δ 156.3, 135.9, 129.1, 128.1, 122.1, 100.9, 71.5, 68.2, 45.6, 29.9; Análisis Elemental Calculado para C₁₀H₁₂BrNO₂·HCl: C, 40.77; H, 4.44; N, 4.75. Enc.: C, 40.77; H, 4.63; N, 4.63.

Procedimiento general para la preparación de 2-amino-3-(fenil sustituido)-propanol:

124
195

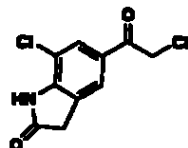
-Butil éster de ácido (S)-[2-(3-bromo-fenil)-1-hidroximetil-etil]-carbamico: A una solución de ácido (S)-3-bromo-fenil)-2-tert-butoxicarbonilamino-propínico (500 mg, 1,45 mmol) en THF (30 ml) se agregó complejo de borano-tetrahidrofurano (solución 1,0 M) (4,35 ml, 4,35 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 14 h y se apagó con ácido acético (1 ml). Después de remover la mayoría del solvente, el residuo se extrajo con EtOAc, se lavó con agua salobre, y se secó sobre Na_2SO_4 . Después de concentración, el producto crudo (400 mg, 83%) se utilizó para la siguiente etapa sin purificación. LCMS $(\text{M}+\text{H})^+$ m/z 330 (t = 1,61 min



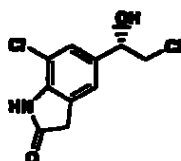
(S)-2-amino-3-(3-bromo-fenil)-propan-1-ol: A una solución de tert-butyl ester de ácido (S)-[2-(3-bromo-fenil)-1-hidroximetil-etil] carbamico (400 mg, 1,21 mmol) en metanol (30 ml) se agregó a HCL 4 M en dioxano (2 ml exceso). La mezcla de reacción se agitó a temperatura ambiente durante 14 h. Después de concentración in vacuo,

~~175~~
196

el residuo se utilizó para la siguiente etapa sin purificación LCMS (M+H)⁺ m/z 230 (t = 0,78 min.)



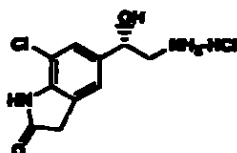
5-cloroacetil-7-clorooxindol: A una suspensión de AlCl₃ (13,4 g, 0,10 mol) en cloruro de metileno (40 ml) se agrega una solución de 7-clorooxindol (0,10 mol) y cloruro de cloroacetil (8 ml, 0,10 mol) a 0°C. La solución se calienta a temperatura ambiente durante 2 horas y se vierte sobre hielo y se extrae con cloruro de metileno, lavando con solución de bicarbonato saturada, agua salobre, y secando sobre MgSO₄, suministraría la clorocetona deseada.



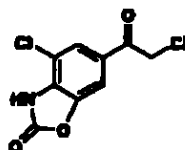
(S)-7-cloro-5-(2-cloro-1-hidroxi-etil)-2-oxoindol: A una solución de (S)-metil-CBS-oxaborolidino (1 M en tolueno, 0,745 ml, 0,745 mmol) y BH₃-THF (8 ml, 8 mmol) se agrega al mismo tiempo una solución de BH₃-THF (19 ml, 19 mmol) y una solución de 5-cloroacetil-7-clorooxindol (37,98 mmol) en 19 ml de THF. Ambas soluciones se agregan

176
197

gota a gota durante 30 minutos. La solución se agita durante 1 hora y se apaga con adición lenta de metanol (50 ml). La solución se concentra y el residuo se cromatografía sobre una columna corta de sílica gel 1:1 hexano/etil acetato.

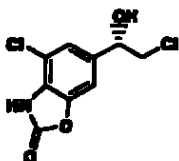


Clorhidrato de (S)-2-amino-1-(7-clorooxindol-5-il)-etanol: a una solución de la clorohidrina (37, 9 mmol) en 120 ml de metanol a -40°C se agrega 100 gramos de amonio. La solución se sella en una botella a presión y se calienta a temperatura ambiente y se agita durante 48 horas. La solución se enfría y se abre. El amonio se le permite evaporarse y la solución se concentra para suministrar la sal de clorhidrato, que se puede cristalizar de etanol/etil acetato.



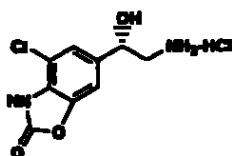
127
198

6-cloroacetil-4-cloro-2-benzooxazolinona: A una suspensión de AlCl_3 (13,4 g, 0,10 mol) en cloruro de metileno (40 ml) se agregó una solución de 4-cloro-2-benzooxazolinona (0,10 mol) y cloruro de cloroacetilo (8 ml, 0,10 mol) a 0°C . La solución es calentada temperatura ambiente durante dos horas y vertida en hielo y se extrajo con cloruro de metileno, lavando con solución de bicarbonato saturado, solución salina, y secado sobre MgSO_4 , suministrará la clorocetona deseada.

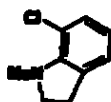


(S)-6-(2-Cloro-1-hidroxi-etil)-4-cloro-2-benzooxazolinona: A una solución de (S)-Metil-CBS-oxazaborolidina (1M en tolueno, 0,745 ml, 0,745 mmol) y BH_3 -THF (8 ml, 8 mmoles) se agregó al mismo tiempo una solución de BH_3 -THF (19 ml, 19 mmol) y una solución de el 6-cloroacetil-4-cloro-2-benzooxazolinona (37,98 mmoles) en 19 ml de THF. Ambas soluciones se agregan gota a gota durante 30 minutos. La solución se agita durante una hora y se apaga con adición lenta de metanol (50 ml). La solución se concentró y el residuo se cromatografió sobre una columna de sílica gel corta (1:1 hexano/acetato de etilo).

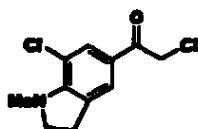
128
199



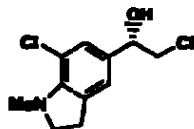
Clorhidrato de (S)-2-Amino-1-(4-cloro-2-benzooxazolinona-6-il)-etanol: A una solución de clorohidrina (37,9 mmoles) en 120 ml en 120 ml de metanol a -40° C se agregó 100 gramos de amonio. La solución es sellada en una botella a presión y calentada a temperatura ambiente y agitada durante 48 horas. La solución es enfriada y abierta. Al amonio se le permitió evaporar y la solución se concentró para dar la sal de hidrocloruro, que puede ser cristalizada a partir de etanol/acetato de etilo.



N-Metil-7-cloroindolino: A una solución de 7-cloroindol (0,10 mol) en 500 ml de acetona se agrega K_2CO_3 (0,15 mol) y MeI (0,15 mol) y se refluje hasta que se consume el material de partida. La reacción se filtra y se lava con agua y solución de bicarbonato saturada, secando sobre $MgSO_4$ suministraría el N-Me-7-cloroindolino.

174
200

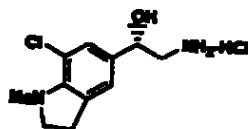
N-metil-5-cloroacetil-7-cloro-indol: A una suspensión de AlCl_3 (13,4 g, 0,10 mol) en cloruro de metileno (40 ml) se agrega una solución de N-Me-7-cloroindol (0,10 mol) y cloruro de cloroacetilo (8 ml, 0,10 mol) a 0°C . La solución se calienta a temperatura ambiente durante 2 horas y se vierte sobre hielo y se extrae con cloruro de metileno, lavando con solución de bicarbonato saturado, agua salobre, y secado sobre MgSO_4 suministra la clorocetona deseada.



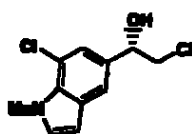
(S)-N-metil-5-(2-cloro-1-hidroxietil)-7-cloro-indol: A una solución de (S)-metil-CBS-oxazaborolidina (1M en tolueno, 0,745 ml, 0,745 mmol) y $\text{BH}_3\text{-THF}$ (8 ml, 8 mmol) se agrega al mismo tiempo una solución de $\text{BH}_3\text{-THF}$ (19 ml, 19 mmol) y una solución de N-metil-5-cloroacetil-7-cloro-indolino (37,98 mmol) en 19 ml de THF. Ambas soluciones se agregaron gota a gota durante 30 minutos. La solución es agitada durante 1 hora y apagada con la adición lenta

201

de metanol (50 ml). La solución se concentra en residuo cromatografiado sobre columna corta de sílica gel (1:1 hexano/acetato de etilo).



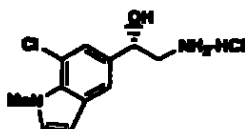
Clorhidrato de (S)-2-amino-1-(7-cloro-N-metil-indolino-5-il)-etanol: A una solución de la clorhidrina (37,9 mmol) en 120 ml de metanol a -40°C se agregan 100 gramos de amonio. La solución se sella en una botella de presión y se calienta a temperatura ambiente y se agita durante 48 horas. La solución se enfría y se abre. El amonio se le permite evaporarse y la solución se concentra para suministrar la sal de clorhidrato, que se puede cristalizar de etanol/etil acetato.



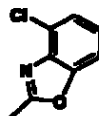
(S)-2-cloro-1-(7-cloro-N-metil-indol-5-il)-etanol: A una solución de (S) -N-metil-5-(2-cloro-1-hidroxietil)-7-cloro-indolino (0,10 mmol) en 100 ml de t-butil metil

181
202

éter se trata con o-cloroanil (0,10 mmol) a temperatura ambiente. La solución se concentra y el residuo se cromatografía sobre sílica gel (1:1 hexano/etil acetato) para suministrar el indol correspondiente.



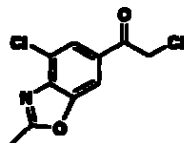
Clorhidrato de (S)-2-amino-1-(7-cloro-N-metil-indol-5-il)-etanol: A una solución de clorhidrina (37,9 mmol) en 120 ml de metanol a -40°C se agregan 100 gramos de amonio. La solución se sella en una botella de presión y se calienta a temperatura ambiente y se agita durante 48 horas. La solución se enfría y se abre. Al amonio se le permite evaporarse y la solución se concentra para suministrar la sal de clorhidrato, la cual se puede cristalizar del etanol/acetato de etilo.



4-cloro-2-metil-benzooxazol: A una solución de 4-cloro-2-benzooxazolinona (0,10 mol) en 200 ml, de etano,

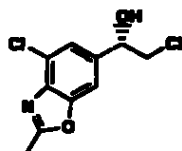
/ 82
203

se agrega LiOH (0,20 mol) en 100 ml de agua. La solución se refluje durante 8 horas y se enfría. La solución se neutraliza con HCl 1N y se extrae con acetato de etilo fluido al secar sobre MgSO₄. La solución se concentra y se toma en 200 ml de tolueno y 0,10 mol de ácido acético. La solución se refluje en una trampa Dean Stara durante 12 horas concentrada y purificada mediante cromatografía de destello.

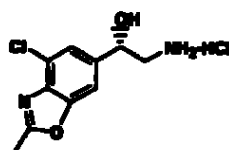


6-Chloroacetil-4-cloro-2-metil-benzooxazol: A una suspensión de AlCl₃ (13,4 g, 0,10 mol) en cloruro de metileno (40 ml) se agrega una solución de 2-metil-4-cloro-benzooxazol (0,10 mol) y cloruro de cloroacetilo (8 ml, 0,10 mol) a 0°C. La solución se calienta a temperatura ambiente durante 2 horas y se vierte sobre hielo y se extrae con cloruro de metileno, lavando con solución de bicarbonato saturado, agua salobre, y secando sobre MgSO₄ suministraría la clorocetona deseada.

27
204



(S)-6-(2-cloro-1-hidroxi-etil)-4-cloro-2-metil-benzooxazol: A una solución de (S)-metil-CBS-oxazaborolidina (1M en tolueno, 0,745 ml, 0,745 mmol) y BH_3 -THF (8 ml, 8 mmol) se agrega al mismo tiempo una solución de BH_3 -THF (19 ml, 19 mmol) y una solución de 6-cloroacetil-4-cloro-2-metil-benzooxazol (37,98 mmol) en 19 ml de THF. Ambas soluciones se agregan gota a gota durante 30 minutos. La solución es agitada durante 1 hora y apagada con la adición lenta de metanol (50 ml). La solución se concentra y el residuo se cromatografía sobre una columna corta de sílica gel (1:1 hexano/acetato de etilo).

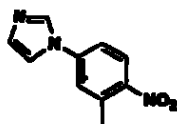


Clorhidrato de (S)-2-amino-1-(4-cloro-2-metil-benzooxazol-6-IL)-etanol: A una solución de la clorhidrina (37,9 mmol) en 120 ml de metanol a -40°C se agregan 100 gramos de amonio. La solución se sella en una botella de presión y se calienta a temperatura ambiente y

134
205

se agita durante 48 horas. La solución se enfría y se abre. Al amonio se le permite evaporarse y la solución se concentra para suministrar la sal de clorohidrato, la cual se puede cristalizar de etanol/etil acetato.

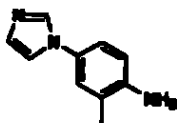
Preparación de 3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-yodo-1H-piridin-2-ona:



1-(3-metil-4-nitro-fenil)-1H-imidazol: A una solución de 4-fluoro-2-metil-1-nitro-benzeno (300 mg, 1,84 mmol) en DMSO (2 ml) se agregó KOH (20 mg, 3,87 mmol) e imidazol (263 mg, 3,88 mmol). La mezcla de reacción se calentó a 100°C durante 3,5 h, se enfrió a temperatura ambiente, y se diluyó con hielo-agua fría. El precipitado resultante se filtró se lavó con hielo-agua fría y se secó bajo vacío para dar el compuesto del título (310 mg, 80%) como un polvo amarillo. ¹H-RMN (300 MHz,

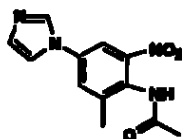
DMSO-d₆) δ 8.46 (1H, s), 8.16 (1H, d, J = 8.9 Hz), 7.90 – 7.92 (2H, m), 7.78 (1H, dd, J = 2.5, 8.9 Hz), 7.17 (1H, s), 2.61 (3H, s). LRMS (M+H)⁺ m/z 204.

AS
206



4-imidazol-1-il-2-metil-fenilamina: A 1-(3-metil-4-nitro-fenil)-1H-imidazol (200 mg, 0,98 mmol) y 10% de paladio sobre carbono (35 mg) se agregó metanol desgasificado (3 ml). La suspensión se reflujo y se evacuó con hidrogeno/linea de vacío. La suspensión se le permitió agitarse temperatura ambiente durante 14 horas bajo atmósfera de hidrógeno (balón de hidrógeno). La mezcla de reacción es oscura se filtró a través de una almohadilla de celita y se enjuagó con metanol. La concentración del filtrado dio el compuesto del título (166 mg, 98%) la cual se utilizó para la siguiente etapa sin purificación.

¹H NMR (300 MHz, DMSO-d₆) δ 7.95 (1H, s), 7.48 (1H, s), 7.16 (1H, angosto d, J = 2.5 Hz), 7.09 (1H, dd, J = 2.5, 8.4 Hz), 7.01 (1H, s), 6.67 (1H, d, J = 8.4 Hz), 5.03 (2H, Ancho s), 2.10 (3H, s).



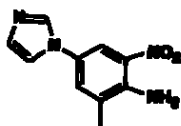
N-(4-Imidazol-1-il-2-metil-6-nitro-fenil)-acetamida:
A una solución de 4-imidazol-1-il-2-metil-fenilamina (1 g, 5,78 mmol) en CH₂Cl₂ (20 ml) se agregó Ac₂O (0,7 ml,

26
207

7,28 mmol) a 0° C. La mezcla de reacción se agitó a temperatura ambiente durante 14 h y se diluyó con agua. La capa acuosa se extrajo con CH₂Cl₂ y las capas orgánicas combinadas se lavaron con NaHCO₃ saturado y agua salobre, se secó sobre Na₂SO₄, y se concentró in vacuo para dar un sólido blanco. El sólido blanco se suspendió en H₂SO₄ (conc.) (15 ml). Luego el HNO₃ (conc.) (312 ml) se agregó a la suspensión a 0°C. La mezcla de reacción se calentó lentamente a temperatura ambiente y se agitó a temperatura ambiente durante 4 h. Después de enfriar a -10°C, la mezcla de reacción se neutralizó con hidróxido de amonio y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua salobre, se secaron sobre Na₂SO₄ y se concentraron. El residuo se purificó mediante cromatografía de destello (1:9:5 MeOH/THF/hexano) para producir el compuesto del título (0,61 g, 41%).

¹H NMR (300 MHz, CD₃OD) δ

8.11 (1H, s), 7.45 – 7.56 (2H, m), 7.38 (1H, dd, J = 2.4, 8.4 Hz), 7.14 (1H, s), 2.33 (3H, s), 2.18 (3H, s).

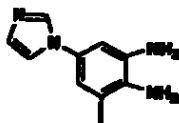


4-imidazol-1-il-2-metil-6-nitro-fenilamina: A una suspensión de N-(4-imidazol-1-il-2-metil-6-nitro-fenil)-

22
208

acetamida (279 mg, 1,07 mmol) en etanol (3 ml) se agregó 2 N HCl (2 ml). La mezcla de reacción se calentó a reflujo durante 14 h, se enfrió a temperatura ambiente, y se neutralizó con NaHCO₃. El sodio resultante naranja brillante se filtró y se secó bajo vacío. El compuesto del título (179 mg, 76%) se obtuvo como un sólido naranja.

¹H NMR (300 MHz, CD₃OD) δ 8.78 (1H, s), 8.24 (1H, s), 7.78 (1H, s), 7.64 (1H, s), 7.46 (1H, s), 2.36 (3H, s).

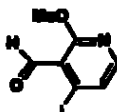


5-imidazol-1-il-3-metil-benzeno-1,2-diamina: a 4-imidazol-1-il-2-metil-6-nitro-fenilamina (350 mg, 1,61 mmol) y 10% de paladio sobre carbono (40 mg) se agregó metanol desgasificado (5 ml) y TFA (5 gotas), La mezcla de reacción se reflujo y se evacuó con hidrógeno/linea de vacío, se agitó temperatura ambiente durante 14 h bajo atmósfera de hidrógeno (balón de hidrógeno). La mezcla de reacción oscura se filtró a través de una almohadilla de celite y se enjuagó con etanol. La concentración del filtrado dio el residuo, el cual se diluyó con agua, se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con NaHCO₃, saturado, agua salobre,

38
209

se secaron sobre Na_2SO_4 . La concentración hasta que se dio el compuesto del título (275 mg, 91%) como un sólido.

^1H NMR (300 MHz, CD_3OD) δ 7.87 (1H, s), 7.34 (1H, s), 7.05 (1H, s), 6.72 (1H, d, J = 2.4 Hz), 6.65 (1H, d, J = 2.4 Hz) 2.21 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 189 (t = 0.23 min.).



4-yodo-2-metoxi-piridina-3-carbaldehido

(wo

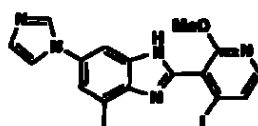
95/29917): A un recipiente de 5 litros con tres cuellos de fondo redondeado se equipo con un agitador mecánico de sobre cabeza bajo nitrógeno, el recipiente se cargo con THF (1L) y se enfrió a -78°C . A esta solución agitada se agregó tert-butililitio (1,7 M solución en pentano) (800 ml, 1,36 mol) vía cánula seguido por 2-metoxipiridina (132, 2 g, 1,21 mol) a -78°C . La mezcla se agitó durante 1 h a -78°C . A la mezcla se agregó N-formil-N, N', N'-trimetiletilenodiamina (176 ml, 1,37 mmol) gota a gota a -78°C . La mezcla de reacción se agitó para ca por 30 min a -78°C antes de calentar a -23°C sobre ca. 30 min. A la mezcla a -23°C se le agregó etileno glicol de dimetil eter (1 l) seguido por N-butilitio (2,5 M solución en hexano) (800 ml, 2,0 mol). La mezcla resultante se agitó para ca. 2 h tiempo durante el cual la mezcla de reacción se volvió un verde profundo. A un recipiente de 12 l de 4

2/0

cuellos redondo se cargó con yodo (571 g, 2, 25 mol) y etileno glicol y metil eter (2 l) y la solución resultante se enfrió a -78°C . Los contenidos del recipiente de 5 l se transfirieron vía cánula a la mezcla de yodo y etilenglicol dimetil eter en el recipiente de 12 l a -78°C . Después de que la adición se completó la mezcla de reacción se agitó durante 1 hora adicional a -78°C . El paño de enfriamiento se removi6 y a la mezcla se le permitió calentarse a aproximadamente 0°C y se trat6 con 2 L de agua y 2 L de ácido clorhídrico 1N. Se agregó metil t-butil éter (2L) y las capas se separaron. La capa acuosa se extrajo con 2 x 1 L de metil t-butil eter. Las capas orgánicas combinadas se lavaron con Na_2SO_3 saturado (1, 2L), agua salobre (1,2 L), se secaron sobre Na_2SO_4 . Después de concentración in vacuo, la lechada espesa se diluyó con hexano (1 L). La mezcla se enfrió con hielo/baño de agua para ca. 30 min. El precipitado se filtr6 y se sec6 in vacuo para producir el compuesto del título en un sólido amarillo claro.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 10.22 (s, 1H), 7.86 (1H, d, $J =$

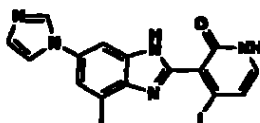
5.3 Hz), 7.54 (1H, d, $J = 5.3$ Hz), 4.06 (3H, s). LCMS ($\text{M}+\text{H}^+$) m/z 364 ($t = 2.26$ min.).



193
211

6-imidazol-1-il-2-(4-yodo-2-metoxi-piridin-3-il)-4-metil-1H-benzimidazol: A una solución de 5-imidazol-1-il-3-metil-benzeno-1,2-diamina (175 mg, 0,93 mmol) en metanol (8 ml) se agregó una solución de 4-yodo-2-metoxi-piridina-3-carbaldehído (245 mg, 0,93 mmol) en metanol (5 ml) a 0°C. la mezcla de reacción se agitó a 0°C durante 1, 5 h y luego a temperatura ambiente durante 2 h. Después de concentración, el residuo se purificó mediante cromatografía de columna de destello (10% MeOH/CH₂Cl₂) para dar el compuesto del título (291 mg, 60%).

¹H NMR (300 MHz, CD₃OD) δ 8.13 (1H, s), 7.98 (1H, d, J = 5.4 Hz), 7.62 (1H, d, J = 5.4 Hz), 7.59 (2H, s), 7.33 (1H, s), 7.16 (1H, s), 3.90 (3H, s), 2.67 (3H, s). LCMS (M+H)⁺ m/z 432 (t ≈ 0.99 min.).



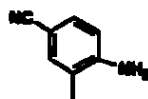
3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-yodo-1H-piridin-2-ona: La suspensión de 6-imidazol-1-il-2-(4-yodo-2-metoxi-piridin-3-il)-4-metil-1H-benzimidazol en HCl 1N (6 ml) se calentó a 70°C durante 3 días, se enfrió a temperatura ambiente y se diluyó con acetato de etilo. Después de la extracción las capas orgánicas combinadas se agregaron con agua salobre, se secaron sobre Na₂SO₄ y se

f 11
212

concentraron. El residuo se purificó mediante cromatografía de destello (1% NH₄OH/10% MeOH/CH₂Cl₂) para producir el compuesto del título (78 mg, 81%) como un sólido.

¹H NMR (300 MHz, CD₃OD) δ 8.12 (1H, s), 7.58 (2H, s), 7.29 – 7.31 (2H, m), 7.16 (1H, s), 7.01 (1H, J = 6.8 Hz), 2.66 (3H, s).
LCMS (M+H)⁺ m/z 418 (t = 0.75 min.)

Preparación 2-(4-cloro-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzemidazol-5-carbonitrilo:

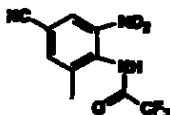


4-amino-3-metil-benzonitrilo: A una solución de 3-metil-4-nitro-benzonitrilo (20 g, 0,123 mol) en HOAc (200 ml) se agregó polvo de hierro (17,55 g, 0,309 mol). Después de 10 min, la reacción fue exotérmica y se volvió de color oscuro. La mezcla de reacción se le permitió agitarse a temperatura ambiente durante 14 h y luego se diluyó con EtOAc (200 ml) el precipitado café se filtró a través de una almohadilla de celita y la torta de filtro se enjuagó con EtOAc. El filtrado se concentró in vacuo y el recibo se purificó mediante cromatografía de destello

H
213

(40% EtOAc/hexano) para producir el compuesto del título (15,3 g, 92%).

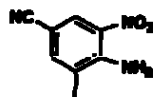
^1H NMR (300 MHz, CDCl_3) δ 7.30 – 7.34 (2H, m), 6.64 (1H, d, $J = 8.7$ Hz), 2.16 (3H, s). LCMS ($\text{M} + \text{H}$) $^+$ m/z 133 ($t = 0.93$ min).



N-(4-ciano-2-metil-6-nitro-fenil)-2,2,2-trifluoro-acetamida: Al hielo-anhidrido trifluoroacético frío (60 ml) se agregó 4-amino-3-metil-benzonitrilo (14, 33g, 0,108 mol) en porción. La lechada blanca resultante se agitó a 0°C durante 30 min. Luego se agregó nitrato de amonio (17,28 g, 0,216 mol). La mezcla de reacción se le permitió agitarse a 0°C durante 1 h y a temperatura ambiente durante 14 h. Después de la remoción de la mayoría del solvente, la mezcla de reacción se enfrió con hielo y se apagó con hielo. El precipitado amarillo se filtró, se lavó con agua fría y se secó bajo vacío. El producto crudo (15,5 g, 52% de rendimiento, y ca. 80% de pureza) se utilizó para la siguiente etapa sin purificación.

H₂
214

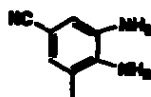
¹H NMR (300 MHz, CD₃OD) δ 8.05 (1H, s), 7.74 (1H, s), 2.30 (3H, s).
LRMS (neg. ESI, (M-H)⁻) m/z 272.



4-amino-3-metil-5-nitro-benzonitrilo: Una mezcla de N-(4-ciano-2-metil-6-nitro-fenil)-2,2,2-trifluoroacetamida (5 g, 18,3 mmol) y amonio 2 M en metanol (80 ml) se calentaron a reflujo durante 14 h y luego se enfriaron a temperatura ambiente. Después de concentración in vacuo, el residuo se purificó mediante cromatografía de destello (20% EtOAc/hexano) para producir el compuesto del título (3,24 g, 100%, ca 80% de pureza).

¹H NMR

(300 MHz, CDCl₃) δ 8.40 (1H, s), 7.47 (1H, s), 6.6–6.8 (2H, Amplio s), 2.89 (3H, s).



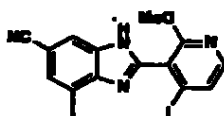
3,4-diamino-5-metil-benzonitrilo: A una solución de 4-amino-3-metil-5-nitro-benzonitrilo (3,24 g, 18,3 mmol) en etanol (80 ml) se agregó dihidrato de cloruro de

1-4
215

estaño (8,67 g, 49,75 mmol). La mezcla de reacción se calentó hasta reflujo durante 14 h, luego se enfrió a temperatura ambiente, y se concentró in vacuo. El residuo se diluyó con acetato de etilo (100 ml) y se trató con trietilamina (20 ml). La lechada resultante se filtró a través de una almohadilla de celita y la torta de filtro se enjuagó con tres porciones de acetato de etilo (50 ml). El filtrado se lavó con NaHCO₃ agua, agua salobre, y se secó sobre NaSO₄ y se filtró. Después de remoción del solvente, el residuo se purificó mediante cromatografía de destello sobre sílica gel (30%-50% de EtOAc/hexano) para producir el compuesto del título (2,17 g, 81%) como un sólido amarillo claro.

¹H NMR (300 MHz, CDCl₃)

δ 6.94 (1H, s), 6.85 (1H, s), 2.16 (3H, s). LCMS (M+H)⁺ m/z 148 (t = 0.67 min.).



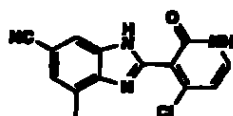
2-(4-yodo-2-metoxi-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo: A una solución de 3,4-diamino-5-metil-benzonitrilo (2,00 g, 13,6 mmol) en MeOH (40 ml) se agregó 4-yodo-2-metoxi-piridina-3-carbaldehído (3,6 g, 13,6 mmol) en MeOH (20 ml) a 0° C. La lechada

216

resultante se agitó a 0°C durante 1 h. Se agregó yodo (1,73 g, 8,8 mmol) en MeOH (10 ml) gota a gota por vía de un embudo de goteo a la mezcla de reacción de 0° C. La mezcla de reacción se agitó a temperatura ambiente durante 14 h. Después de la remoción del MeOH, el residuo se diluyó con Na₂S₂O₃ saturado y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y agua salobre, se secaron sobre Na₂SO₄. El producto crudo se purificó mediante cromatografía de columna de destello (3% MeOH/CH₂Cl₂) para producir el compuesto del título (1,81 g, 46%).

¹H

NMR (300 MHz, CDCl₃) δ 7.90 (1H, s), 7.49 (1H, d, J = 5.4 Hz), 7.46 (1H, s), 7.41 (1H, d, J = 5.3 Hz), 3.78 (3H, s), 2.68 (3H, s). LCMS (M+H)⁺ m/z 391 (t = 1.27 min.).

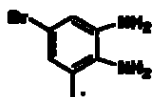


2-(4-cloro-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo: Una suspensión de 2-(4-yodo-2-metoxi-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo (1,8 g, 4,63 mmol) en 4 M HCl dioxano (40 ml) se calentó a 80° C durante 6 h y se enfrió a temperatura ambiente. El precipitado se filtró y se secó. El producto crudo (1,08 g, 82%) se utilizó para la

f96
217

siguiente etapa sin purificación. LRMS (neg. ESI, (M-H)⁻) m/z 283.

Preparación de (S)-4-(1-benzil-2-tritiloxi-etilamino)-3-(6-bromo-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:



5-bromo-3-metil-benzeno-1,2-diamina: A una suspensión de 4-bromo-2-metil-6-nitro-fenilamina (20 g, 0,086 mol) en etanol (200 ml) se agregó hidrato de cloruro de estaño (49,2g, 0,258 mol). La mezcla de reacción se calentó a reflujo durante 14 h, se enfrió a temperatura ambiente, y se concentró in vacuo. El residuo se diluyó con acetato de etilo (150 ml) y se trató con trietilamina (40 ml). La lechada resultante se filtró a través de una almohadilla de celita, y la torta de filtro se enjuagó con 3 porciones de acetato de etilo de (50 ml). El filtrado se lavó con NaHCO₃ saturado, agua y agua salobre, luego se secó sobre NaSO₄ y se filtró. Después de la remoción del solvente, el residuo se purificó mediante cromatografía de destello sobre sílica gel (30% EtOAc/hexano, luego 5% MeOH/CH₂Cl₂) para producir el

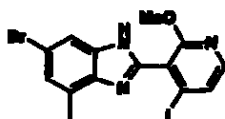
197
218

compuesto del título (10,26 g, 59%) como un aceite amarillo.

¹H NMR

(300 MHz, CDCl₃) δ 6.77 (1H, d, *J* = 2.0 Hz), 6.74 (1H, d, *J* = 2.0 Hz), 2.16 (3H, s).

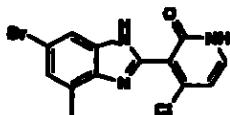
LCMS (M+H)⁺ *m/z* 201. (*t* = 0.83 min.).



6-bromo-2-(4-yodo-2-metoxi-piridin-3-il)-4-metil-1H-benzimidazol: A una solución de 5-bromo-3-metil-1,2-fenilenodiamina (4 g, 19,9 mmol) en metanol (80 ml) se agregó 4-yodo-2-metoxi-piridina-3-carbaldehído (5,23 g, 19,9 mmol) en metanol (20 ml) gota a gota a 0°C. La lechada resultante se agitó durante 30 minutos a temperatura ambiente. Luego yodo (2,53 g, 9,95 mmol) en metanol (20 ml) se agregaron por vía de un embudo de goteo. Después de 14 h, la mezcla de reacción se concentró in vacuo, se diluyó con Na₂S₂O₃ al 5% y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua, agua salobre, y se secaron Na₂SO₄. Después de la remoción del solvente, el residuo se purificó mediante cromatografía de destello cuidadosa (20% EtOAc/hexano) para producir el compuesto del título (4,05 g, 46%) como una espuma amarilla.

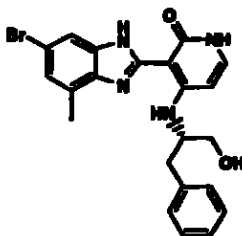
48
219

¹H NMR (300 MHz, CDCl₃) δ 7.86 (1H, d, *J* = 5.31 Hz), 7.53 (1H, d, *J* = 5.3 Hz), 7.26 (2H, Amplio s), 3.91 (3H, s), 2.63 (3H, s). LCMS (M+H)⁺ *m/z* 444 (*t* = 1.39 min.).



3-(6-Bromo-4-metil-1H-benzimidazol-2-il)-4-cloro-1H-piridin-2-ona: La suspensión de 6-bromo-2-(4-yodo-2-metoxi-piridin-3-il)-4-metil-1H-benzimidazol (4 g, 9,03 mmol) y 60 ml de HCL 4 M en dioxano se calentaron a 80°C durante 6 h y se enfriaron a temperatura ambiente. El precipitado se filtró y se secó para producir el compuesto del título (3,0 g, 100%) como un polvo café. El producto crudo se utilizó para la siguiente etapa sin purificación.

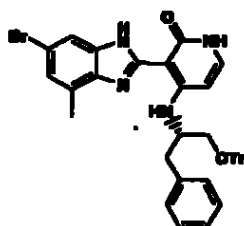
¹H NMR (300 MHz, CD₃OD) δ 7.55 (1H s), 7.42 (1H, d, *J* = 6.0 Hz), 7.17 (1H, s), 6.91 (1H, d, *J* = 6.0 Hz), 2.55 (3H, s). LC MS (M+H)⁺ *m/z* 338 (*t* = 1.33 min.).



1-49
220

(S)-4-(1-benzil-2-hidroxi-etilamino)-3-(6-bromo-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona: A una solución de 3-(6-bromo-4-metil-1H-benzimidazol-2-il)-4-cloro-1H-piridin-2-ona (1,42 g, 3,78 mmol) en DMF (15 ml) se agregó (S)-(-)-2-amino-3-fenilo-1-propanol (1,43 g, 9,45 mmol) y N-metil morfolino (1,5 ml). La mezcla de reacción se calentó a 80°C durante 6 h y se enfrió a temperatura ambiente. El solvente se removió con alto vacío y el residuo se purificó mediante cromatografía de destello (5% MeOH/CH₂Cl₂) para producir el compuesto del título (1,26 g, 74%) como una espuma amarilla.

¹H NMR (300 MHz, CDCl₃) δ 6.9 – 7.2 (8H, m), 5.86 (1H, d, *J* = 7.1 Hz), 3.7-3.9 (3H, m), 2.9-3.1 (2H, m), 2.57 (3H, s). LCMS (*M*+*H*)⁺ *m/z* 453 (*t* = 2.03 min.).



(S)-4-(1-benzil-2-tritiloxi-etilamino)-3-(6-bromo-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona: A una solución de (S)-4-(1-benzil-2-hidroxi-etilamina)-3-(6-bromo-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona (0,9 g, 1,98 mmol) en THF (30 ml), se agregó Cs₂CO₃ (1,29 g,

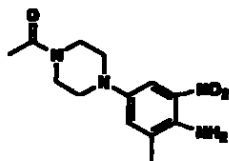
221

3,96 mmol) seguido por cloruro de trifenilmetilo (1,10 g, 3,96 mmol). La mezcla de reacción se calentó hasta reflujo durante 14 h bajo nitrógeno y luego se enfrió a temperatura ambiente. Después de la remoción del solvente, el residuo se diluyó con acetato de etilo y se lavó con agua. La fracción acuosa se extrajo con acetato de etilo y las capas orgánicas combinadas se lavaron con agua y agua salobre, se secaron sobre Na_2SO_4 . Después de la concentración in vacuo, el residuo se purificó mediante cromatografía de columna de destello (30% EtOAc/hexano) para producir el compuesto del título (1 g, 73%) como un sólido blanco.

^1H NMR (300 MHz, DMSO-d_6) δ 11.77 (1H Amplio s), 11.73 (1H, d, $J = 5.2$ Hz), 11.46 (1H, Ampl. s), 7.13 – 7.54 (23H, m), 5.87 (1H, d, $J = 4.5$ Hz), 4.09 – 4.14 (1H, m), 3.07 – 3.42 (4H, m), 2.54 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 695 ($t = 2.79$ min.).

Preparación de 3-[6-(4-acetil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-cloro-1H-piridin-2-ona:

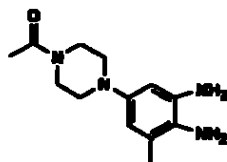
222



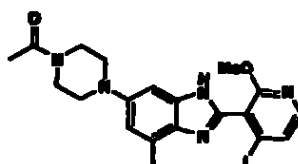
1-[4-(4-Amino-3-metil-5-nitro-fenil)-piperazin-1-il]-etanona: Una mezcla de 4-bromo-2-metil-6-nitro-fenilamina (5 g, 21,64 mmol), 1-acetilpiperazina (4,2 g, 32,46 mmol), acetato de paladio (244 mg, 1,08 mmol), tri-tert-butilfosfina (440 mg, 2,16 mmol) y tert-butoxido de sodio (4,2 g, 43, 29 mmol) en tolueno (70 ml) se calentaron a 100°C durante 14 h bajo nitrógeno. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con EtOAc. Después de la extracción, las capas orgánicas combinadas se lavaron con agua, agua salobre, se secaron sobre Na₂SO₄. La concentración dio un residuo café que se purificó mediante cromatografía de columna de destello (10% MeOH/CH₂Cl₂) para producir el compuesto del título (4,21 g, 70%).

¹H NMR (400 MHz, CD₃OD) δ 7.42 (1H, d, J = 2.8 Hz), 7.23 (1H, d, J = 2.8 Hz), 3.71 (2H, t, J = 5.1 Hz), 3.67 (2H, t, J = 5.1 Hz), 3.04 (2H, t, J = 5.2 Hz), 2.98 (2H, t, J = 5.2 Hz), 2.24 (3H, s), 2.13 (3H, s). LCMS (M+H)⁺ m/z 279 (t = 1.46

223

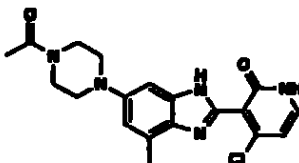


1-[4-(3,4-Diamino-5-metil-fenil)-piperazin-1-il]-etanona: A 1-[4-(4-amino-3-metil-5-nitro-fenil)-piperazin-1-il]-etanona (4,5 g, 16, mmol) y 10% de paladio sobre carbono (400 mg) se agregó metanol (50 ml) y ácido acético (5 ml) bajo nitrógeno. La mezcla de reacción se agitó bajo atmósfera de hidrógeno (balón de hidrógeno) durante 14h. La solución oscura se filtró a través de una almohadilla de celita y la torta de filtro se lavó con metanol. La concentración del filtrado dio el compuesto del título (4,00 g, 100%) que se utilizó para la siguiente etapa sin purificación. LCMS (M+H)⁺ m/z 207 (t = 0,41 min.).



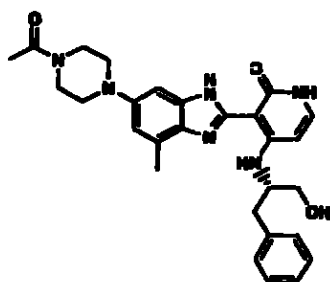
1-{4-[2-(4-yodo-2-metoxi-piridin-3-il)-7-metil-3H-benzimidazol-5-il]-piperazin-1-il}-etanona: A una solución de 1-[4-3,4-diamino-5-metil-fenil)-piperazin-1-il]-etanona (4,00 g, 16,18 mmol) en metanol (100 ml) se agregó 4-yodo-2-metoxi-piridina-3-carbaldehído (4,25 g, 16, 18 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 14 h. Después de

concentración, el residuo se purificó mediante cromatografía de columna de destello (10% MeOH/CH₂Cl₂) para producir el compuesto del título (5,25 g, 66%).



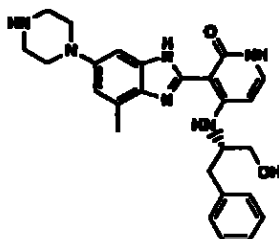
3-[6-(4-acetil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-cloro-1H-piridin-2-ona: A una solución de 1-{4-[2-(4-yodo-2-metoxi-piridin-3-il)-7-metil-3H-benzimidazol-5-il]-piperazin-1-il}-etanona (5,2 g, 10,6 mmol) en 4 HCL 4 M en dioxano (60 ml) se agregó agua (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 14 h. La concentración de la mezcla de reacción dio el compuesto del título (4,02 g, 100%) que se utilizó para la siguiente etapa sin purificación. LCMS (M+H)⁺ m/z 486 (t = 1,55 min).

Preparación de (S)-4-[1-hidroximetil-2-fenil-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona:

224
225

(S)-3-[6-(4-acetil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona: A una solución de 3-[6-(4-acetil-piperazin-1-il)-4-metil-1H-benziminazol-1-il]-4-cloro-1H-piridin-2-ona (1 gmmol) en DMF (10 ml) se agregó (S)-(-)-2-amino-3-fenil-propanol (0,78 mg, 5,2 mmol) y N-metil morfolino (2 ml). La mezcla de reacción se calentó a 80°C durante 12 h, se enfrió a temperatura ambiente y se concentró con vacío alto. El residuo se purificó mediante cromatografía de columna de destello (10% MeOH/CH₂Cl₂) para producir el compuesto del título (0,90 g, 69%).

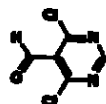
¹H NMR (400 MHz, CD₃OD) δ 7.36 (1H, s), 7.02 – 7.23 (6H, m), 6.80 (1H, s), 5.98 (1H, d, *J* = 7.5 Hz), 4.10 – 4.12 (3H, m), 3.67 – 3.78 (6H, m), 3.06 – 3.11 (3H, m), 2.90 (1H, dd, *J* = 7.8, 13.6 Hz), 2.54 (3H, s), 2.12 (3H, s). LCMS (M+H)⁺ *m/z* 501 (*t* = 1.30 min.).



V. 226

(S)-4-(1-hidroximetil-2-fenil-etilamino)-3-4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona:
 A una solución de (S)-3-[6-(4-acetil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridina-2-ona (900 mg, 18 mmol) en HCL 4 M en dioxano (10 ml) se agregó agua (1 ml). La mezcla de reacción se calentó a 80°C durante 14 h y se enfrió a temperatura ambiente. La concentración con vacío alto dio el compuesto del título (0,83 g, 100%) y tal fue utilizado para la siguiente etapa sin purificación. LCMS (M+H)+ m/z 459 (t=1,13 min).

Preparación de 2-(4,6-Dicloro-piridin-5-il)-6-imidazol-1-il-4-metil-1H-benzimidazol:



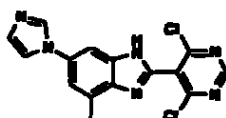
4,6-Dicloro-pirimidina-5-carbaldehído: DMF (7 ML, 0,09 mol) se agregó a POCl₃ (21 ml, 0,21 mol) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 0,5 h. Se agregó 4,6-dihidroxi-pirimidina-5-carbaldehído (5 g, 0,045 mol) en porciones pequeñas. La mezcla de reacción se calentó a 90°C durante 6 h y se enfrió a temperatura ambiente. Un gran exceso de hielo

227

molido se agregó a la mezcla de reacción muy lentamente bajo un baño de hielo. La mezcla se extrajo con CH_2Cl_2 . Las capas orgánicas combinadas se lavaron con agua, agua salobre, y se secaron sobre Na_2SO_4 . Después de concentración, el residuo se purificó mediante cromatografía de columna (20% EtOAc/hexano) para producir el compuesto del título (4 g, 50%).

^1H NMR (400 MHz, CDCl_3) δ 8.91

(1H, s), 7.87 (1H, s). LRMS ($\text{M}+\text{H}$) $^+$ m/z 177.



2-(4,6-Dicloro-pirimidin-5-il)-6-imidazol-1-il-4-metil-1H-benzimidazol: A una solución de 5-imidazol-1-il-3-metil-benzeno-1,2-diamina (180 mg, 0,96 mmol) en metanol (4 ml) se le agregó a una solución de 4,6-dicloro-pirimidina-5-carbaldehído (183 mg, 0,96 mmol) en metanol (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 14 h. Después de concentración, el residuo se purificó mediante cromatografía de columna de destello (5% metanol/ CH_2Cl_2)

227
228

Ejemplos 45 - 383 se prepararon de acuerdo a los métodos generales descritos anteriormente (Esquema III)

Condiciones LCMS:

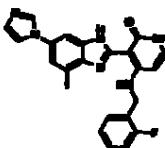
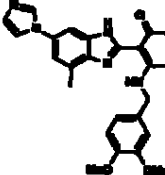
- a) YMC C18 s5 4,6 X 50 mm; 0-100% gradiente durante 4 min*; índice de flujo 4 ml/min
- b) YMC ODS-A C218 S7 3,0 x 50 mm; 0-100% gradiente durante 2 min*; índice de flujo 5 ml/min
- c) YMC C18 S5 4,5 x 50 mm; 0-100% gradiente durante 8 min*; índice de flujo 2 ml/min
- d) YMC C 18 S7 3,0 x 50 mm; gradiente 0 - 100% durante 3 min*; índice de flujo 5 ml/min
- e) YMC ODSA S3 6,0 x 150 mm; gradiente 0 - 100% durante 5 min*; índice de flujo 1,5 ml/min
- f) PHS-PRIMESPHERE C18 4,6 x 30 mm; gradiente 0 - 100% durante 2 min*; índice de flujo 5 ml/min
- g) YMC C 18 S7 3,0 x 50 mm; gradiente 0 - 100% durante 4 min*; índice de flujo 5 ml/min
- h) YMC ODS-A C18 S7 3,0 x 50 mm; gradiente 0 - 100% durante 2 min*; índice de flujo 5 ml/min
- i) YMC ODS-A C18 S7 3,0 x 50 mm; gradiente 0 - 100% durante 1,5 min*; índice de flujo 5 ml/min
- j) YMC Xterra C18 S7 3,0 x 50 mm; gradiente 0 - 100% durante 2 min*; índice de flujo 5 ml/min

229

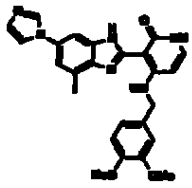
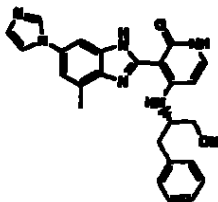
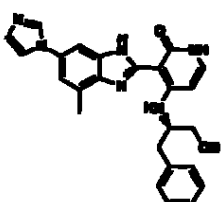
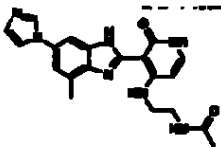
k) YMC Pro-ODS C18 S5 4,6 x 33 mm; gradiente 0 - 100% durante 3 min*; índice de flujo 4 ml/min

l) YMC ODS-A C18 S7 3,0 x 50 mm; gradiente 0 - 100% durante 4 min*; índice de flujo 4 ml/min

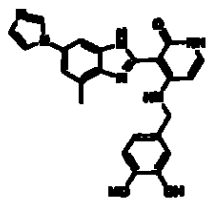
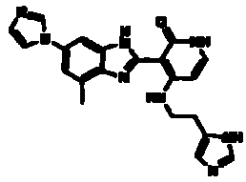
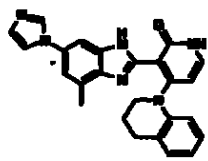
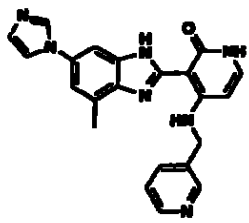
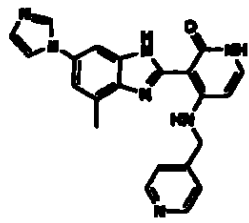
* gradiente el gradiente comienza con 10% de metanol /90% agua (0,1% TFA) y termina con 90% metanol/10% agua (0,1% TFA)

Ej. #	Nombre	Estructura	T (min.)	Masa (M+H) ⁺ m/z
45	4-(2-Fluoro-benzilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,43 (1)	415
46	4-(3,4-Dimetoxi-benzilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,37 (1)	457

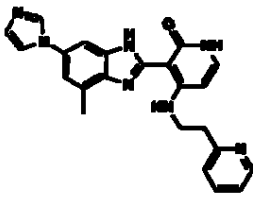
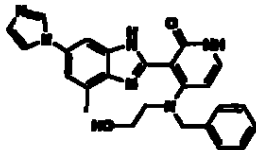
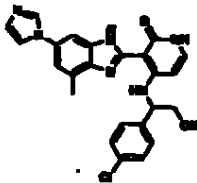
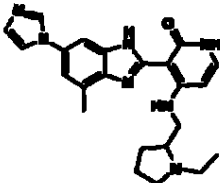
230

47	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(piridin-2-ilmetil)-amino]-1H-piridin-2-ona		2,17(a)	398
48	(S)-4-(1-Hidroximetil-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,48(b)	441
49	(R)-4-(1-Hidroximetil-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,48(b)	441
50	N-{2-[3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-etil}-acetamida		151(1)	392

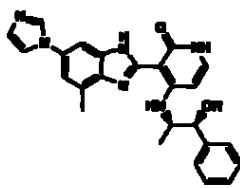
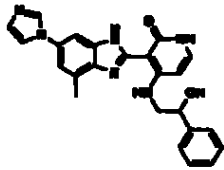
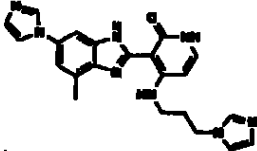
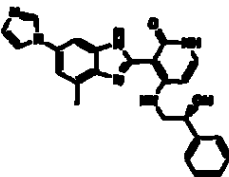
231

51	4-(3,4-Dihidroxi-benzilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,97(1)	429
52	4-[2-(3H-Imidazol-4-il)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,91(a)	401
53	4-(3,4-Dihidro-2H-quinolin-1-il)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,88(a)	423
54	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(piridin-3-ilmetil)-amino]-1H-piridin-2-ona		1,83(a)	398
55	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(piridin-4-ilmetil)-amino]-1H-piridin-2-ona		1,74(a)	398

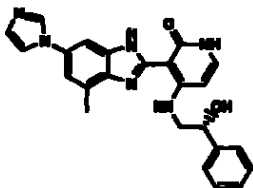
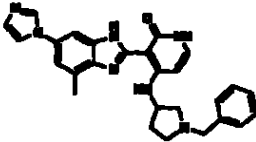
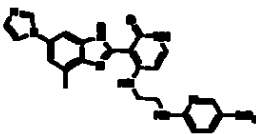
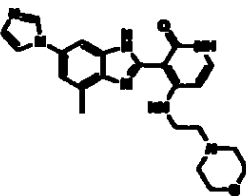
206
232

56	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(piridin-4-ilmetil)-amino]-1H-piridin-2-ona		1,99(a)	412
57	4-[Benzil-(2-hidroxi-etil)-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,86(a)	441
58	(±)-4-[1-(4-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		3,3(a)	461
59	(±)-4-[(1-Etil-pirrolidin-2-ilmetil)-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,88(a)	418

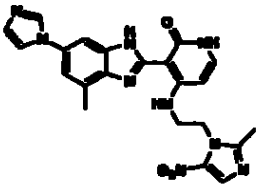
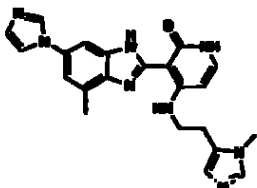
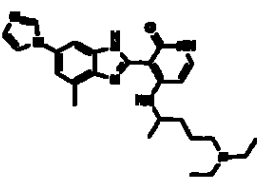
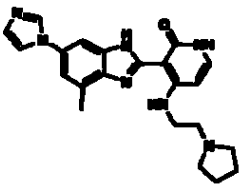
233

60	(1R,2S)-4-(2-Hidroxi-1-metil-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		3,01(a)	441
61	(±)-4-(2-Hidroxi-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		2,96(a)	427
62	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(3-imidazol-1-il-propilaminmo)-1H-piridin-2-ona		1,94(a)	415
63	(S)-4-(2-Hidroxi-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,27(b)	427

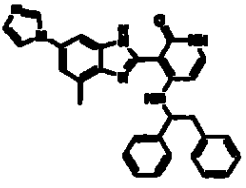
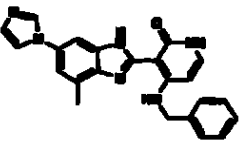
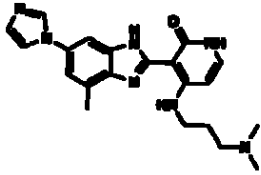
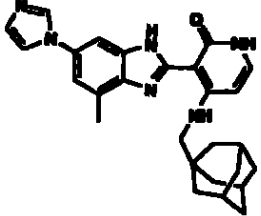
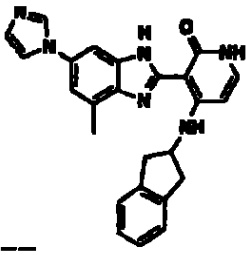
234

64	(R)-4-(2-Hidroxi-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,27(b)	427
65	(±)-4-(1-Benzil-pirrolidin-3-ilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,19(b)	466
66	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[2-(5-nitro-piridin-2-ilamino)-etilamino]-1H-piridin-2-ona		1,37(b)	472
67	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(2-morfolin-4-il-etilamino)-1H-piridin-2-ona		0,98(b)	420

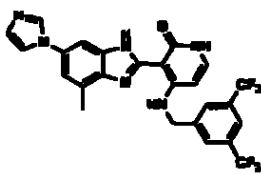
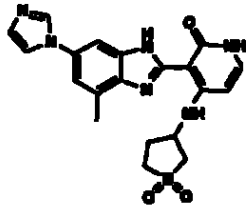
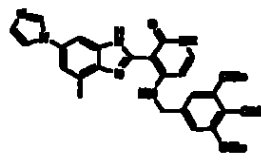
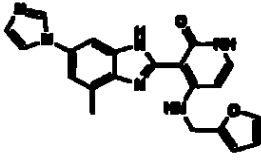
235

68	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[2-(2-metil-5-nitro-1H-imidazol-1-il)-etilamino]-1H-piridin-2-ona		1, 31 (b)	460
69	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[2-(3-metil-3H-imidazol-4-il)-etilamino]-1H-piridin-2-ona		0, 97 (b)	415
70	(±)-4-(4-Dietilamino-1-metil-butilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 13 (b)	448
71	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(2-pirrolidin-1-il-etilamino)-1H-piridin-2-ona		0, 87 (b)	404

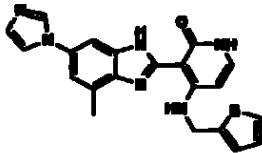
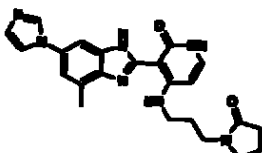
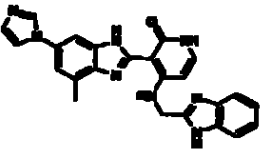
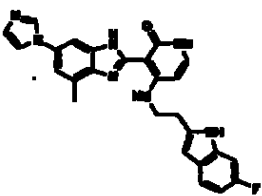
236

72	(±)-4-(1,2-Difenil- etilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1, 72 (b)	487
73	4-Benzilamino-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1, 49 (b)	397
74	4-(3-Dimetilamino- propilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1, 03 (b)	392
75	4[(Adamantan-1- ilmetil)-amino]-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1, 87 (b)	455
76	3-(6-Imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-4-(indan-2- ilamino)-1H-piridin-2- ona		1, 57 (b)	423

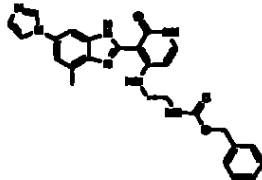
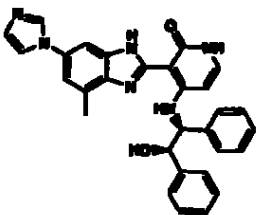
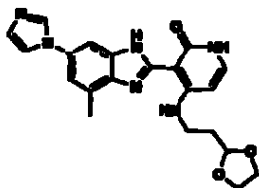
210
237

77	4-(3,5-Bis-trifluorometil-benzilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 68 (b)	533
78	(±)-4-(1,1-Dioxo-tetrahidro-1λ ⁶ -tiofeno-3-ilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 03 (b)	425
79	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(3,4,5-trimetoxi-benzilamino)-1H-piridin-2-ona		1, 33 (b)	487
80	4-[furan-2-ilmetil)-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 34 (b)	387

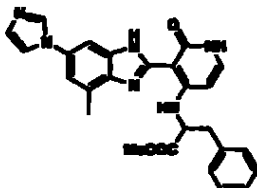
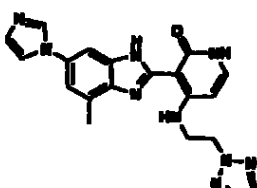
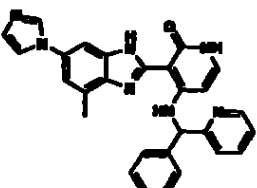
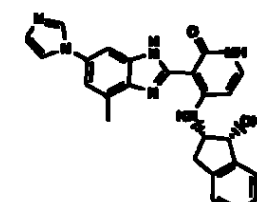
24
238

81	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(tiofen-2-ilmetil)-amino]-1H-piridin-2-ona		1,42(b)	403
82	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[3-(2-oxo-pirrolidin-1-il)propilamino]-1H-piridin-2-ona		1,15(b)	432
83	4-[(1H-Benzimidazol-2-ilmetil)-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		0,98(b)	437
84	4-[2-(6-Fluoro-1H-indol)-2-il)etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,53(b)	468

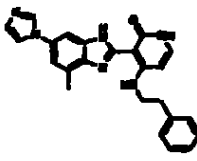
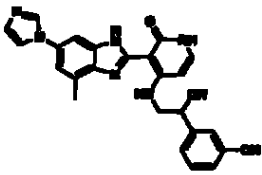
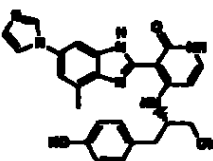
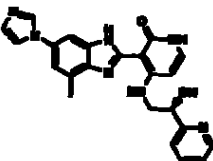
239

85	Ácido {2-[3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 2-oxo-1,2-dihidro- piridin-4-ilamino]- etil)-carbámico benzilo		1,31(b)	484
86	(1S,2R)-4-(2-Hidroxi- 1,2-difenil- etilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,42(b)	503
87	(±)-4-(2-[1,3]- dioxolan-2-il- etilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,24(b)	407

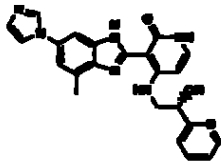
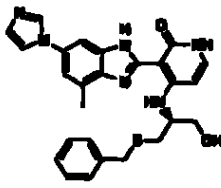
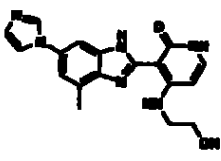
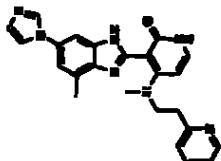
240

88	Ácido (±)-2-[3-(6- Imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 2-oxo-1,2-dihidro- piridin-4-ilamino]-3- fenil-propiónico metil éster		1, 44 (b)	469
89	3-(6-Imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-4-(2-2H- [1,2,3]triazol-2-il- etilamino)-1H-piridin- 2-ona		1, 05 (b)	402
90	(±)-3-(6-Imidazol-1- il-4-metil-1H- benzimidazol-2-il)-4- [(1-fenil-1-piridin-2- il-metil)-amino]-1H- piridin-2-ona		1, 35 (b)	474
91	(1S,2R)-4-(1-Hidroxi- indan-2-ilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1, 35 (b)	439

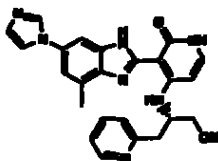
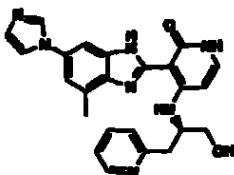
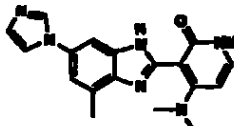
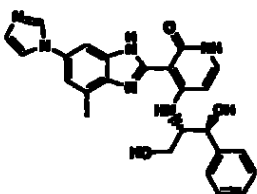
241

92	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-fenetilamino-1H-piridin-2-ona		1,51(b)	411
93	(±)-4-[2-Hidroxi-2-(3-hidroxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,15(a)	443
94	(S)-4-[1-Hidroximetil-2-(4-hidroxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,1(b)	457
95	(R)-4-(2-Hidroxi-2-piridin-2-il-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,09(a)	428

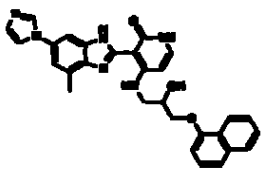
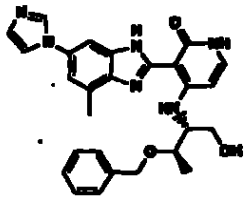
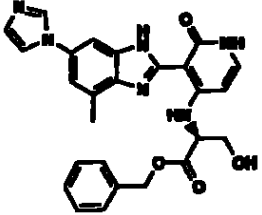
242

96	(S)-4-(2-Hidroxi-2-piridin-2-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,09(a)	428
97	(S)-4-(2-Benzilsulfanil-1-hidroximetil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,4(b)	487
98	4-(2-Hidroxi-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		0,93(b)	351
99	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-[metil-(2-piridin-2-il-etilamino)]-1H-piridin-2-ona		0,43(b)	426

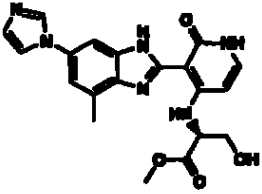
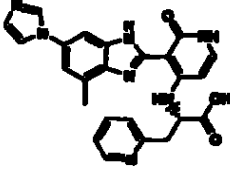
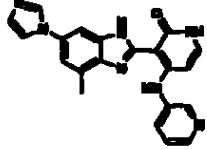
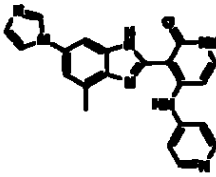
243

100	(S)-4-(1-Hidroximetil- 2-piridin-2-il- etilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		0,93 (f)	442
101	(R)-4-(1-Hidroximetil- 2-piridin-etilamino)- 3-(6-imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-1H-piridin-2-ona		0,94 (f)	442
102	Dimetilamino-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		0,70 (f)	335
103	(1S,2S)-4-(2-Hidroxi- 1-hidroximetil-fenil- etilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,10 (b)	457

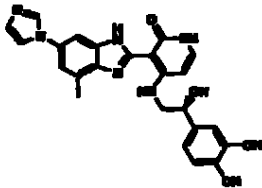
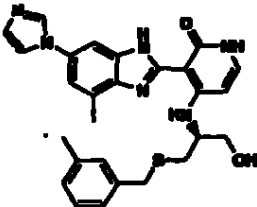
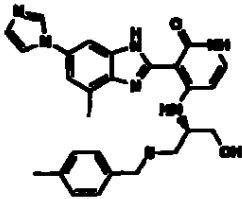
244

104	(±)-4-[2-Hidroxi-3-(naftalen-1-iloxi)-propilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,53(b)	507
105	(1R,2R)-4-(2-Benziloxi-1-hidroximetil-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		3,14(a)	485
106	Ácido (S)-3-Hidroxi-2-[3-(6-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-propiónico benziléster		2,95(a)	485

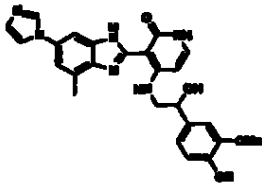
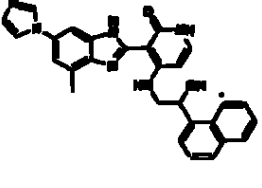
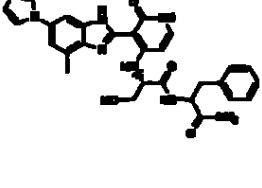
245

107	Ácido (S)-3-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-propiónico metil éster		2,29 (a)	409
108	(S)-2-[3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-3-piridin-2-ona		0,94 (f)	456
109	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(piridin-3-ilamino)-1H-piridin-2-ona		1,15 (a)	384
110	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(piridin-4-ilamino)-1H-piridin-2-ona		0,65 (f)	384

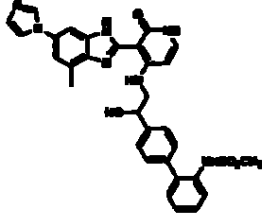
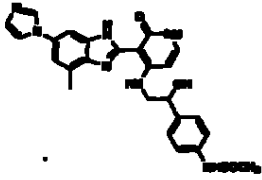
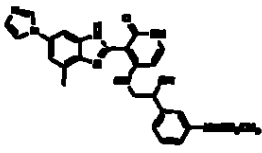
~~246~~
246

111	(S)-4-[2-(3,4-Dihidroxi-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,04(b)	459
112	(S)-4-[1-Hidroxiometil-2-(3-metil-benzilsulfanil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,49(b)	501
113	(S)-4-[1-hidroxiometil-2-(4-metil-benzilsulfanil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,49(b)	501

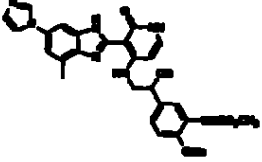
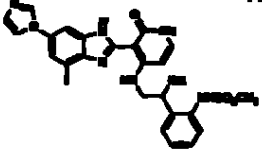
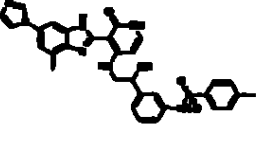


114	(±)-4-[2-Hidroxi-2-(4-hidroxi-3-metoksi-fenil)etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 10 (b)	473
115	4-(2-Hidroxi-2-(naftalen-1-il-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 49 (b)	477
116	(S)-N-(1-carbamoil-2-fenil-etil)-3-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-propionamida		1, 07 (b)	541

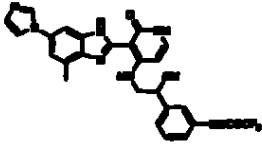
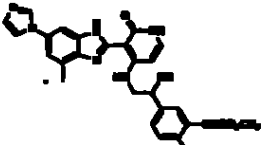
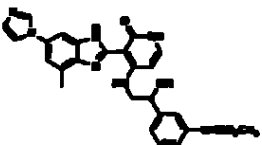
248

117	(±)-N-(4'-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-bifenil-2-il)-metanosulfonamida		1, 34 (b)	596
118	(±)-N-(4-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-metanosulfonamida		1, 11 (b)	520
119	(±)-N-(3-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-metanosulfonamida		1, 14 (b)	520

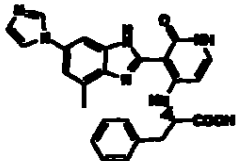
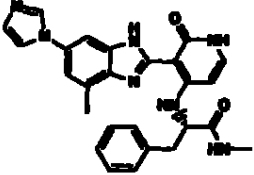
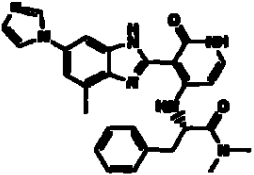
249

120	(±)-N-(5-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-2-metoksi-fenil)-metanosulfonamida		1,12(b)	550
121	(±)-N-(2-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-metanosulfonamida		1,19(b)	520
122	(±)-N-(3-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-4-metil-bencenosulfonamida		1,33(b)	596

22
250

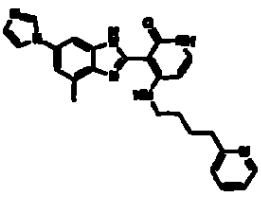
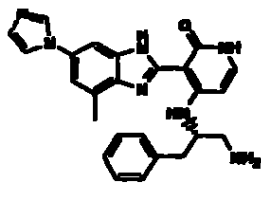
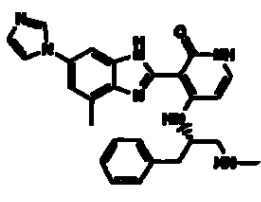
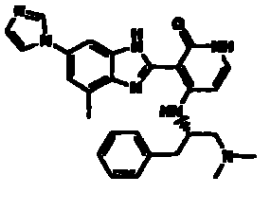
123	(±)-2,2,2-trifluoro-N-(3-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-acetamida		2,97(a)	538
124	(±)-N-(2-Cloro-5-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-metanosulfonamida		2,75(a)	554
125	(±)-N-(5-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-2-metil-fenil)-metanosulfonamida		2,73(a)	534

22*
251

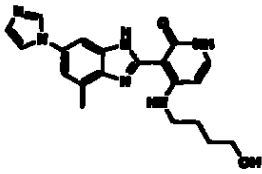
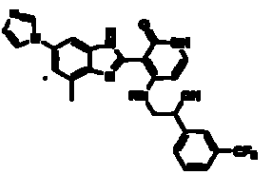
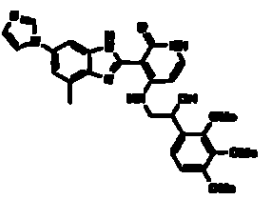
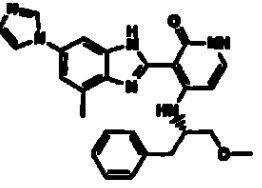
126	Ácido (S)-2-[3-(6- Imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 2-oxo-1,2-dihidro- piridin-4-ilamino]-3- fenil-propiónico		1,50 (f)	455
127	(S)-2-[3-(6-Imidazol- 1-il-4-metil-1H- benzimidazol-2-il)-2- oxo-1,2-dihidro- piridin-4-ilamino]-N- metil-3-metil-3-fenil- propionamida		1,43 (f)	468
128	(S)-2-[3-(6-Imidazol- 1-il-4-metil-1H- benzimidazol-2-il)-2- oxo-1,2-dihidro- piridin-4-ilamino]-3- fenil-propionamida		1,39 (f)	454

252

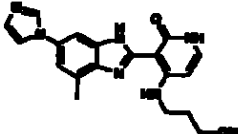
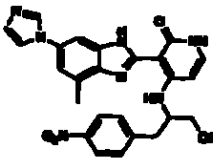
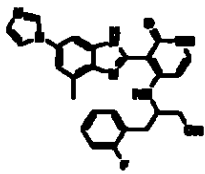
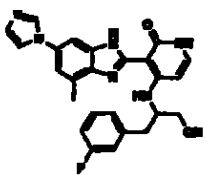
129	(S)-2-[3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-N,N-3-fenil-propionamida		1,48(f)	482
130	(R)-4-(2-Hidroxi-1-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,44(f)	427
131	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(3-piridin-2-il-propilamino)-1H-piridin-2-ona		1,0(b)	426
132	(S)-4-(1-Benzil-4-hidroxi-2-oxo-butilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,41(f)	483

133	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(4-piridin-2-il-n-butilamino)-1H-piridin-2-ona		1,06(d)	440
134	(S)-4-(1-Aminometil-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,27(f)	440
135	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(1-metilaminoetil-2-fenil-etilamino)-1H-piridin-2-ona		1,27(f)	454
136	(S)-4-(1-Dimetilaminometil-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,25(f)	468

254
227

137	4-(4-Hidroxi-butilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,19(f)	379
138	(±)-4-[2-Hidroxi-2-(3-trifluorometil-fenil)-3-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,40(b)	495
139	(±)-4-[2-Hidroxi-2-(3,4,5-trimetoxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,18(b)	517
140	(S)-4-(1-Benzil-2-metoxi-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,97(f)	455

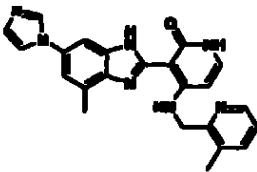
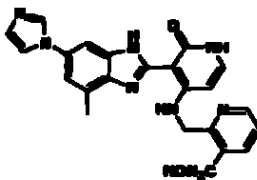
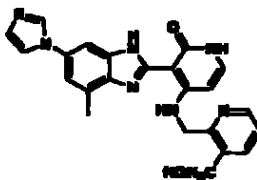
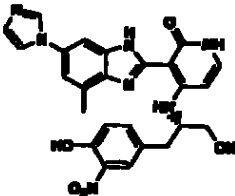
255 

141	4-(3-Hidroxi-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		0,95 (f)	365
142	(±)-4-[2-Hidroxi-1-(4-nitro-benzil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,51 (a)	486
143	(±)-4-[1-(2-Fluoro-benzil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,57 (a)	459
144	(±)-4-[1-(3-Fluoro-benzil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,57 (a)	459

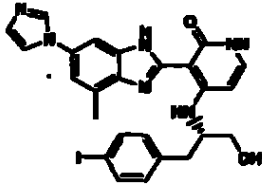
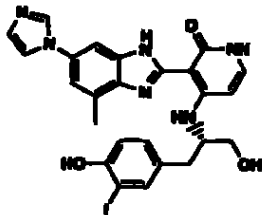
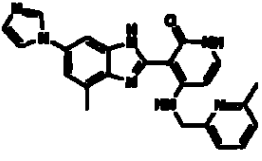
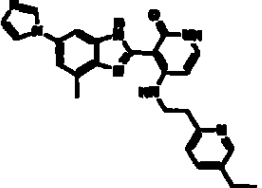
256 224

145	(S)-4-[hidroxi-1-(4-metoxi-benzil)etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,54(a)	471
146	(±)-4-[2-Hidroxi-1-(3-hidroxi-benzil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,38(a)	457
147	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(3-isoquinolin-3-il-metil)-amino]-1H-piridin-2-ona		1,15(d)	448
148	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[[4-(3-fenil-propil)-piridin-2-ilmetil]-amino]-1H-piridin-2-ona		1,31(d)	516

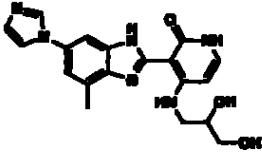
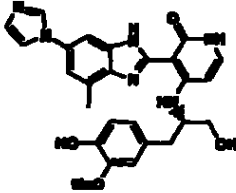
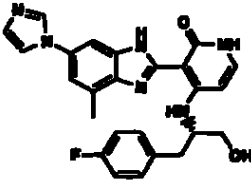
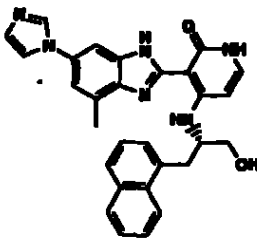
232
257

149	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(3-metil-piridin-2-ilmetil)-amino]-1H-piridin-2-ona		1,00 (d)	412
150	4-[(3,5-Dimetil-piridin-2-ilmetil)-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,00 (d)	426
151	4-[(3-Hidroximetil-piridin-2-ilmetil)-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		0,93 (d)	428
152	(S)-4-[2-Hidroxi-1-(4-hidroxi-3-nitro-benzil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,47 (a)	486

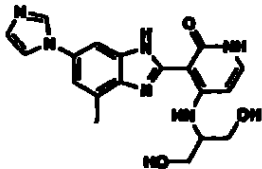
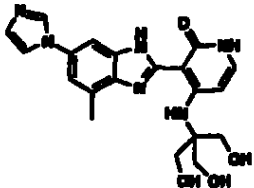
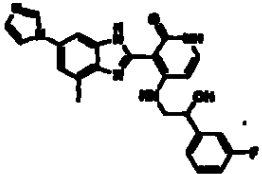
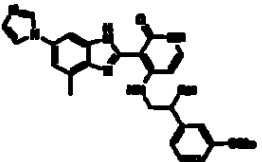
258

153	(S)-4-[2-Hidroxi-1-(4-yodo-benzil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,73(a)	567
154	(S)-4-[2-Hidroxi-1-(4-hidroxi-3-yodo-benzil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,44(a)	583
155	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(6-metil-piridin-2-ilmetil)-amino]-1H-piridin-2-ona		0,71(b)	412
156	4-[2-(5-Etil-piridin-2-il)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,01(b)	440

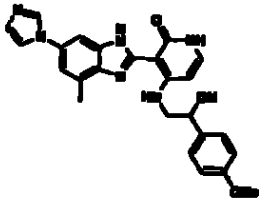
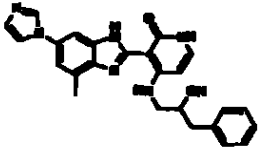
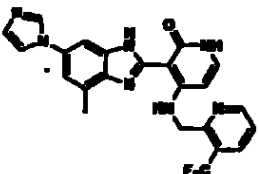
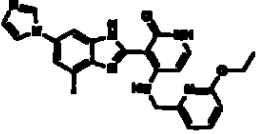
259 232

157	(±)-4-(2,3-Dihidroxi-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,11(a)	381
158	(S)-4-(2-Hidroxi-1-(4-hidroxi-3-metoksi-benzil)-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,29(f)	491
159	(S)-4-[1-(4-Fluorobenzil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,57(a)	459
160	(S)-4-[2-Hidroxi-1-(naftalen-1-il-metil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,71(a)	491

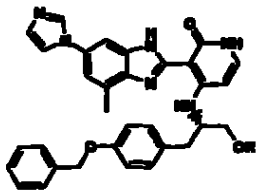
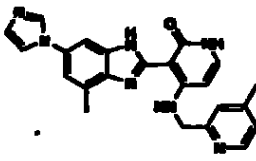
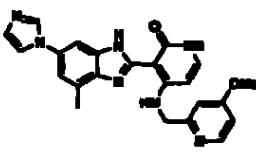
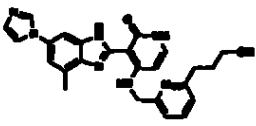


161	4-(2-Hidroxi-1-hidroximetil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,00 (f)	381
162	4-[2-Hidroxi-1,1-bis-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		0,89 (f)	411
163	(±)-4-[2-(3-Fluorofenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,38 (b)	445
164	(±)-4-[2-Hidroxi-2-(3-metoxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,35 (b)	457

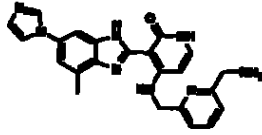
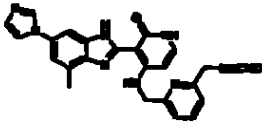
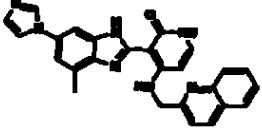
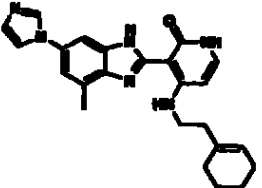
261

165	(±)-4-[2-Hidroxi-2-(4-metoxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 35 (b)	457
166	(±)-4-(2-Hidroxi-3-fenil-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 44 (b)	441
167	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(3-trifluorometil-piridin-2-ilmetil)-amino]-1H-piridin-2-ona		1, 53 (d)	466
168	4-[(6-Etoxi-piridin-2-ilmetil)-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 51 (d)	442

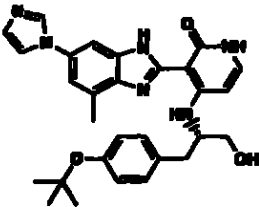
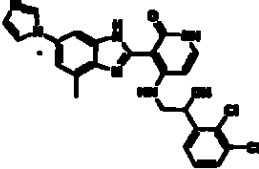
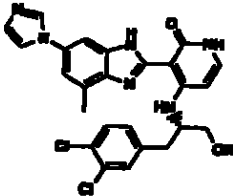
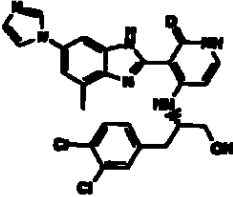
263 9/2/16

173	(S)-4-[1-(4-Benziloxi- benzil)-2-hidroxi- etilamino]-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,74 (f)	547
174	3-(6-Imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-4-[(4-metil- piridin-2-ilmetil)- amino]-1H-piridin-2- ona		0,95 (d)	412
175	3-(6-Imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-4-[(4-metoxi- piridin-2-ilmetil)- amino]-1H-piridin-2- ona		0,92 (d)	428
176	4-{[6-(3-Hidroxi- propil)-piridin-2- iletil]-amino}-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		0,96 (d)	456

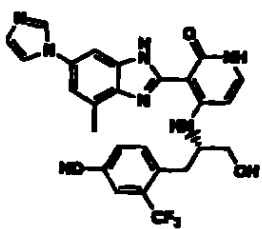
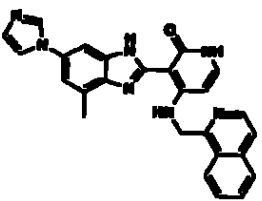
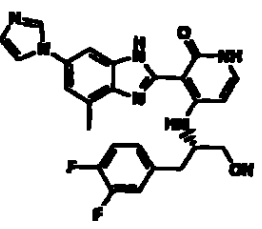
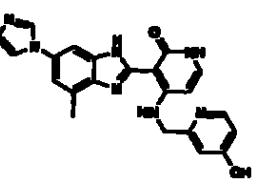
264

177	4-[(6-Aminometil- piridin-2-iletıl)- amino]-3-(6-imidazol- 1-il-4-metil-1H- benzimidazol-2-il)-1H- piridin-2-ona		0,99(b)	427
178	N-(6-[[3-(6-Imidazol- 1-il-4-metil-1H- benzimidazol-2-il)-2- oxo-1,2-dihidro- piridin-4-ilamino]- metil]-piridin-2- ilmetil-formamida		1,02(b)	455
179	3-(6-Imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-4-[(quinolin-2- ilmetil)-amino]-1H- piridin-2-ona		1,16(b)	448
180	4-(2-Ciclihex-1-enil- etilamino)-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,61(b)	415

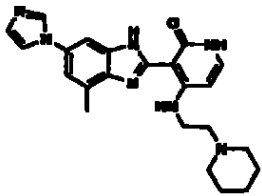
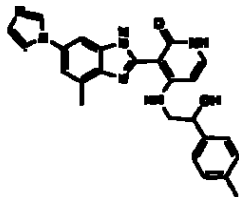
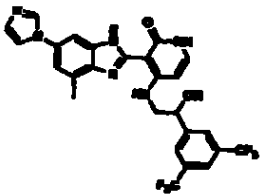
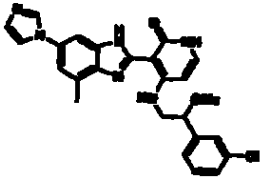
23
265

181	(S)-4-[2-(4-terc-butoxi-fenil)-1-hidroxi-metil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 61 (f)	513
182	(±)-4-[2-(2,3-Dicloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 52 (b)	495
183	(±)-4-[2-(3,4-Difluoro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 34 (b)	463
184	(S)-4-[2-(3,4-Dicloro-fenil)-1-hidroxi-metil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 67 (f)	509

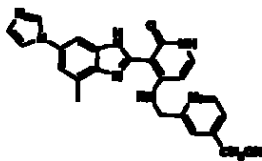
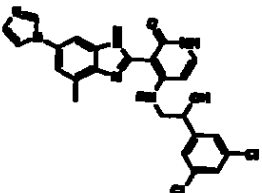
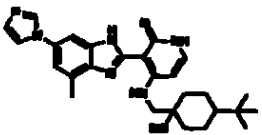


185	(S)-4-[1-Hidroximetil-2-(4-hidroxi-2-trifluorometil-fenil)etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,46(f)	525
186	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(isoquinolin-1-ilmetil)-amino]-1H-piridin-2-ona		1,14(d)	448
187	(S)-4-[2-(3,4-Difluoro-fenil)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,52(f)	477
188	4-[(4-Hidroxi-piridin-2-ilmetil)amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		0,91(d)	414

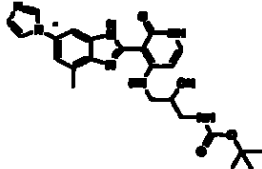
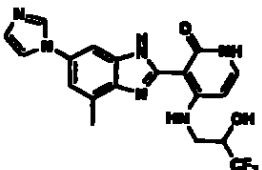
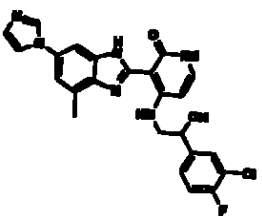
267

189	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(2-piperidin-1-il-etilamino)-1H-piridin-2-ona		0,92 (b)	418
190	(±)-4-(2-Hidroxi-2-p-tolil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		5,74 (c)	441
191	4-[2-(3,5-Bis-trifluorometil-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		6,400	563
192	(±)-4-[2-(3-Cloro-fenil)-2-metoksi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		6,5 (c)	475

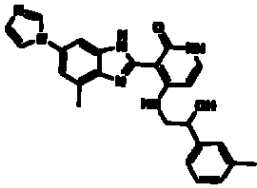
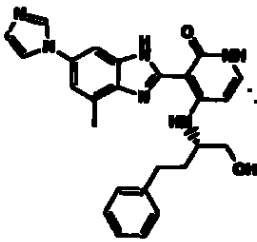
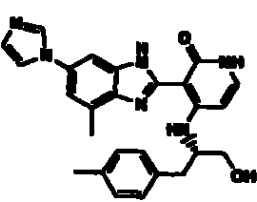
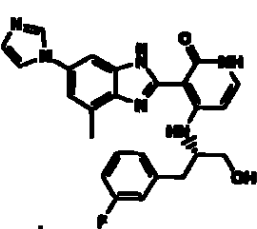
268

193	4-[(4-Hidroximetil- piridin-2-ilmetil)- amino]-3-(6-imidazol- 1-il-4-metil-1H- benzimidazol-2-il)-1H- piridin-2-ona		0,9 (b)	428
194	(±)-4-[2-(3,5-Dicloro- fenil)-2-hidroxi- etilamino]-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,54 (b)	495
195	(±)-4-[(4-terc-Butil- 1-hidroxi- ciclohexilmetil)- amino]-3-(6-imidazol- 1-il-4-metil-1H- benzimidazol-2-il)-1H- piridin-2-ona		3,82 (a)	475

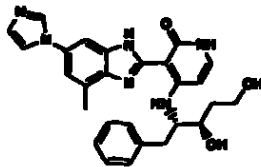
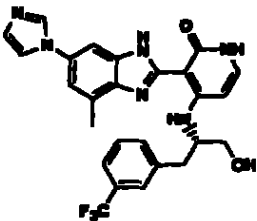
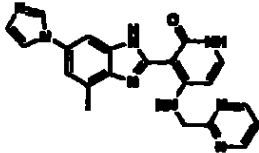
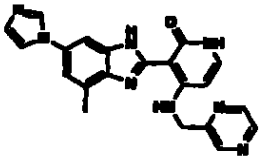
269

196	Ácido (±)-(2-Hidroxi-3-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]propil)carbámico Terc-butiléster		1,23(b)	480
197	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(3,3,3-trifluoro-2-hidroxi-propilamino)-1H-piridin-2-ona		1,17(b)	419
198	(±)-4-[2-(3-Cloro-4-fluoro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,40(b)	479

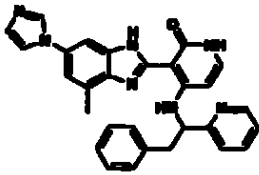
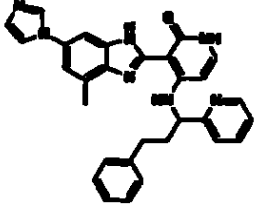
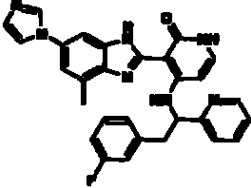
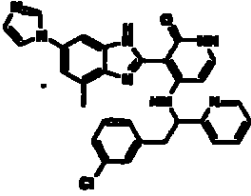
270

199	(±)-4-(2-Hidroxi-2-m-tolil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 37 (b)	441
200	(S)-4-(1-Hidroximetil-3-fenil-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 56 (f)	455
201	(S)-4-(1-Hidroximetil-2-p-tolil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 57 (f)	455
202	(S)-4-[2-(3-Fluorofenil)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 48 (f)	459

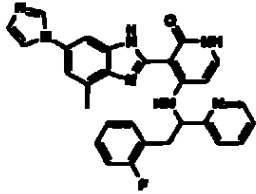
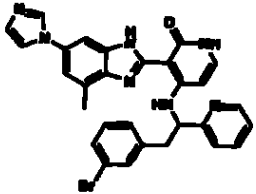
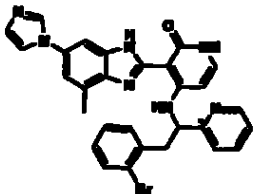
~~271~~
271

203	(1S,2R)-4-(1-Benzil-2,4-dihidroxi-butilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 39 (f)	485
204	(S)-4-[1-Hidroximetil-2-(3-trifluorometil-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 56 (f)	509
205	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(pirimidin-2-ilmetil)-amino]-1H-piridin-2-ona		1, 16 (b)	399
206	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(pirazin-2-ilmetil)-amino]-1H-piridin-2-ona		1, 14 (b)	399

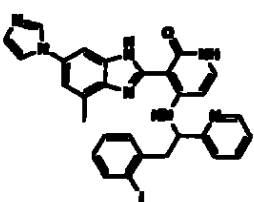
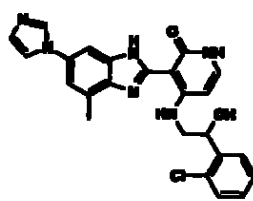
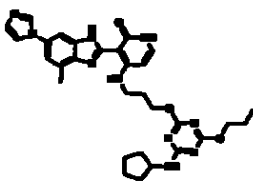
272

207	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(2-fenil-1-piridin-2-il-etilamino)-1H-piridin-2-ona		1,26(b)	488
208	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(3-fenil-1-piridin-2-il-propilamino)-1H-piridin-2-ona		1,34(d)	502
209	(±)-4-[2-(3-Fluorofenil)-1-piridin-2-il-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,31(d)	506
210	(±)-4-[2-(3-Clorofenil)-1-piridinil-2-il-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,39(d)	522

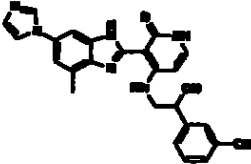
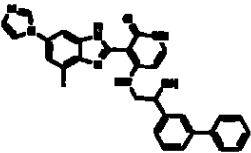
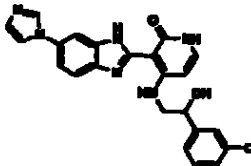
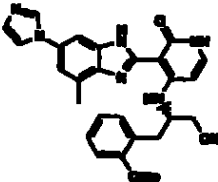
273

211	(±)-4-[2-(2-Fluoro-fenil)-1-piridin-2-il-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,33(d)	506
212	(±)-4-[2-(3-Bromo-fenil)-1-piridin-2-il-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,40(d)	566
213	(±)-4-[2-(2-Bromo-fenil)-1-piridin-2-il-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,45(d)	566

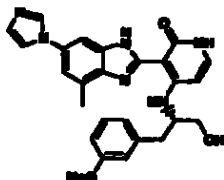
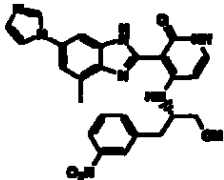
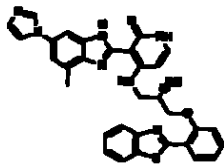
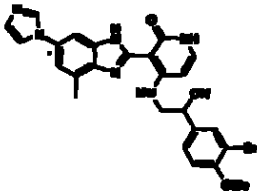
274

214	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[2-(2-yodo-fenil)-1-piridin-2-il-etilamino]-1H-piridin-2-ona		1,47(d)	614
215	(±)-4-[2-(2-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il)-4-metil-1H-benzimidazol-2-il-1H-piridin-2-ona		1,21(i)	461
216	4-[3-(4-Ciclopentilamino-6-propoxi-[1,3,5]triazin-2-iloxi)-propilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,67(b)	585

275

217	(±)-3-[1-Hidroxi-2-[3-(6-imidazol-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil]-benzonitrilo		1,20(b)	452
218	(±)-4-(2-Bifenil-3-il-2-hidroxi-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,51(b)	503
219	(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,35(f)	447
220	(S)-4-[1-Hidroximetil-2-(2-metoxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,52(f)	471

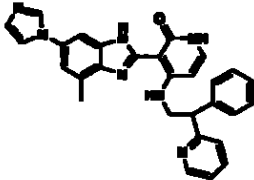
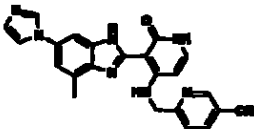
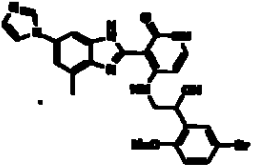
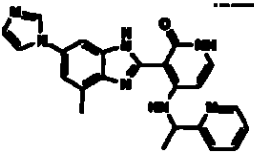
276

221	(S)-4-[1-Hidroxi-metil- 2-(3-metoxi-fenil)- etilamino]-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,42 (f)	471
222	(S)-4-[1-Hidroxi-metil- 2-(3-nitro-fenil)- etilamino]-3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,27 (f)	486
223	(S)-4-[3-(2- Benzotiazol-2-il- fenoxi)-2-hidroxi- propilamino]-3-(6- imidazol-2-il-4-metil- 1H-benzimidazol-2-il)- 1H-piridin-2-ona		1,47 (j)	590
224	(±)-4-[2-(3-Bromo-4- metoxi-fenil)-2- hidroxi-etilamino]-3- (6-imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-1H-piridin-2-ona		1,35 (j)	535

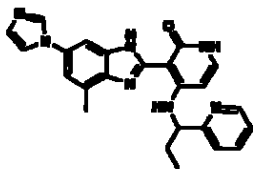
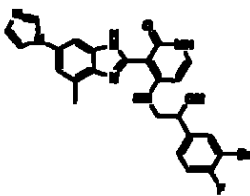
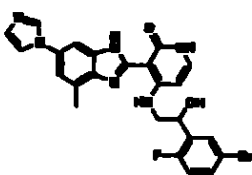
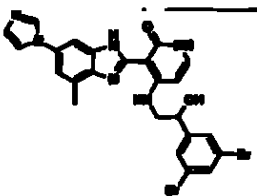
277

225	(S)-4-(1-Benzil-2-hidroxi-2-metil-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		22,07	HPLC
226	(R)-4-(1-Benzil-2-hidroxi-2-metil-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		22,09	HPLC
227	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[(5-metil-piridin-2-ilmetil)-amino]-1H-piridin-2-ona		0,99 (d)	412
228	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(2-fenil-2-piridin-2-il-pent-4-enilamino)-1H-piridin-2-ona		1,41 (d)	528

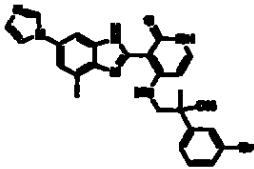
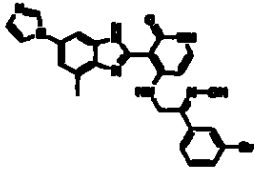
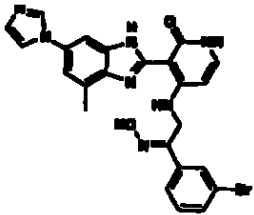
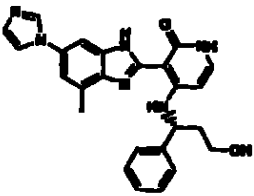
278

229	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(2-fenil-2-piridin-2-il-etilamino)-1H-piridin-2-ona		1,22(d)	488
230	6-([3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-metil)-nicotinonitrilo		1,22(d)	423
231	(±)-4-[2-(5-Bromo-2-metoxi-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,27(i)	535
232	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(1-piridin-2-il-etilamino)-1H-piridin-2-ona		1,12(d)	412

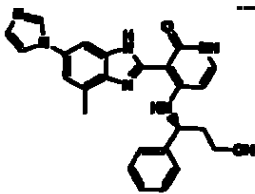
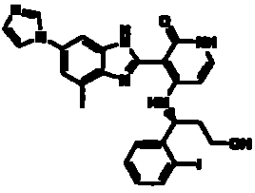
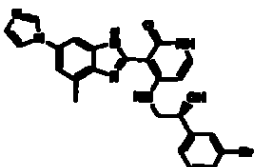
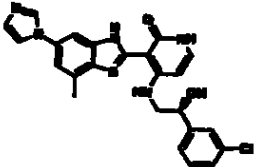
279

233	(±)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(1-piridin-2-il-propilamino)-1H-piridin-2-ona		1,17(d)	426
234	(±)-4-[2-(3-Bromo-4-fluoro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,24(1)	523
235	(±)-4-[2-(5-Bromo-2-fluoro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,15(1)	253
236	(±)-4-[2-(3,5-Dibromo-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,30(1)	583

280

237	(±)-4-[2-(3-Bromo-fenil)-2-hidroxi-propilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,90(d)	519
238	(E)-4-[2-(3-Bromo-4-metoxi-fenil)-2-hidroxiimino]-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		7,81(e)	518
239	(Z)-4-[2-(3-Bromo-fenil)-2-hidroxiimino-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		7,91(e)	518
240	(R)-4-(3-hidroxi-1-fenil-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,48(f)	441

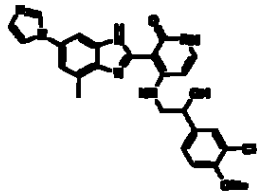
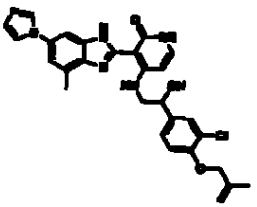
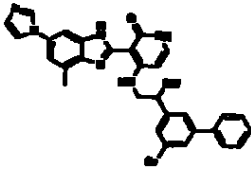


241	(S)-4-(3-Hidroxi-1-fenil-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 48 (f)	441
242	(S)-4-(3-Hidroxi-1-(2-yodo-fenil)-propilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 61 (f)	567
243	(S)-4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 35 (b)	505
244	(S)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 30 (b)	461

282

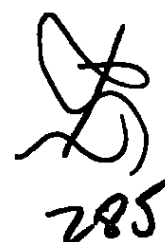
245	(R)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 37 (b)	461
246	(R)-4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 35 (b)	505
247	4-[2-(3-Cloro-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 53 (b)	445
248	(±)-4-[2-(3-Cloro-4-hidroxi-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 15 (b)	477

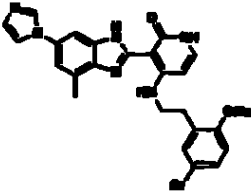
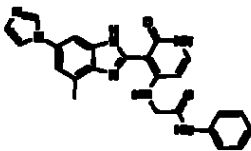
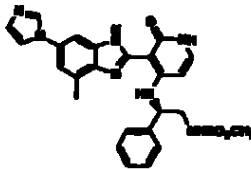
283

249	(±)-4-[2-(3-Cloro-4-metoxi-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 24 (b)	491
250	(±)-4-[2-(3-Cloro-4-(2-metil-aliloxi)-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 46 (b)	531
251	(±)-[2-(5-Bromo-bifenil-3-il)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 44 (i)	581

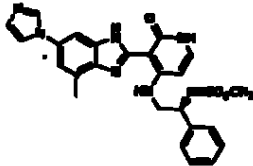
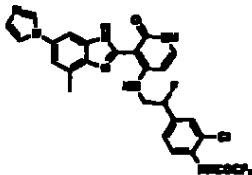
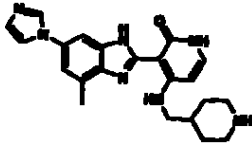
284

252	(±)-4-(2-hidroxi-2-[1,1',3',1'']terfenil-5'-il-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,48(1)	579
253	(±)-4-[2-(3-Cloro-4-propoxi-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,76(b)	519
254	3-[3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-N-fenil-propionamida		1,13(1)	454
255	(±)-4[2-Hidroxi-2-(3-nitro-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,20(1)	472

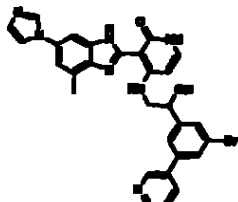
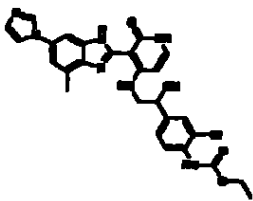
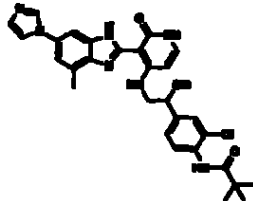


256	4-[2-(5-Bromo-2-metoxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 51 (i)	519
257	2-[3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-N-fenil-acetamida		1, 25 (i)	440
258	(R)-N-{2-[3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-2-fenil-etil}metanosulfonamida		1, 35 (h)	504

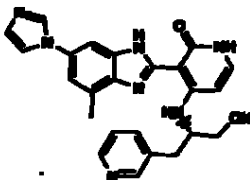
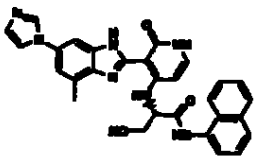
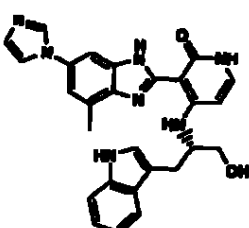
~~286~~
286

259	(S)-N-{2-[3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 2-oxo-1,2-dihidro- piridin-4-ilamino]-1- fenil- etil)metanosulfonamida		1,32(h)	504
260	(±)-N-(2-Cloro-4-{1- fluoro-2-[3-(6- imidazol-1-il-4-metil- 1H-benzimidazol-2-il)- 2-oxo-1,2-dihidro- piridin-4-ilamino]- etil)-fenil)-2,2,2- trifluoroacetamida		1,30(b)	574
261	3-(6-Imidazol-1-il-4- metil-1H-benzimidazol- 2-il)-4-[(piperidin-4- ilmetil)-amino]-1H- piridin-2-ona		0,90(b)	404

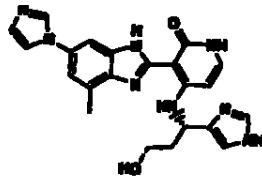
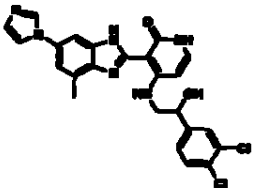
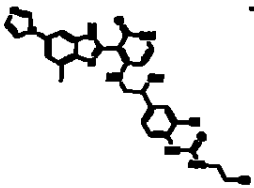
287

262	(±)-4-[2-(3-Bromo-5-piridin-3-il-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,18(a)	582
263	Ácido (±)-(2-Cloro-4-{1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-etil}-fenil)-carbámico etil éster		1,36(b)	548
264	(±)-N-(2-Cloro-4-{1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-etil}-fenil)-2,2-dimetil-propionamida		1,42(b)	560

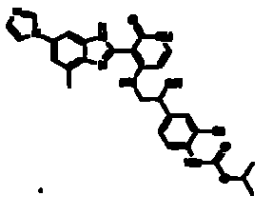
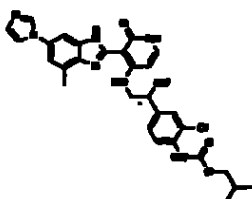
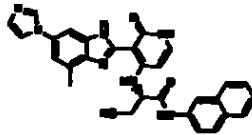
288

265	(S)-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(1-hidroximetil-2-piridin-3-il-etilamino)-1H-piridin-2-ona		0,78 (b)	442
266	(S)-3-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-N-naftalen-1-il-propionamida		1,41 (b)	520
267	(S)-3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[1-(1H-indol-3-ilmetil)-2-hidroxi-etilamiuno]-1H-piridin-2-ona		1,22 (b)	480

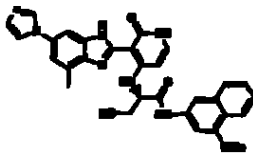
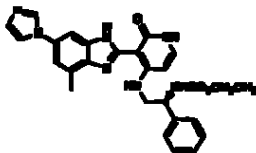
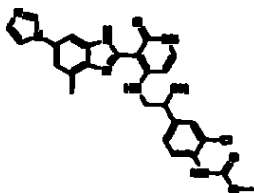
289

268	(S)-4-[3-Hidroxi-1-(imidazol-4-il)-propilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		0,75(b)	431
269	(±)-4-[2-(3,4-Dicloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,48(b)	495
270	(±)-1-(2-Cloro-etil)-3-(2-cloro-4-{1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-etil}-fenil)urea		1,26(b)	581

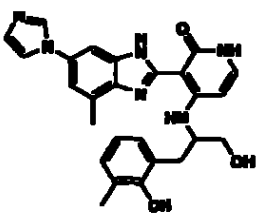
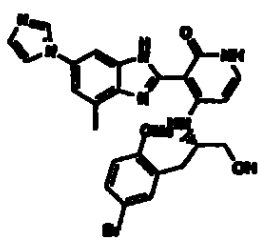
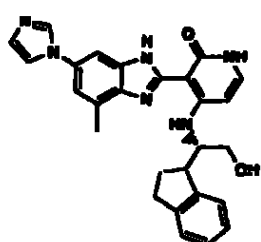
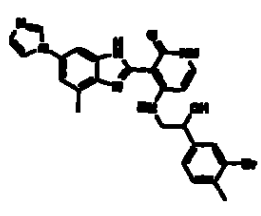
290

271	Ácido (±)-(2-Cloro-4-(1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]etil)-fenil)-carbámico isopropiléster		1,41(b)	562
272	Ácido (±)-(2-Cloro-4-(1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]etil)-fenil)-carbámico isobutiléster		1,49(b)	576
273	(S)-3-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-N-naftalen-2-il-propionamida		1,36(b)	520

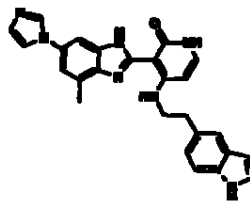
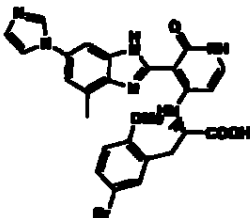
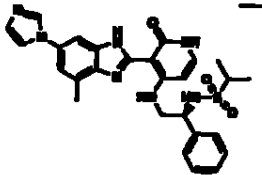
291

274	(S)-3-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-N-(4-metoxi-naftalen-2-il-propionamida		1,45 (b)	550
275	Ácido (S)-Etanosulfónico {2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-1-fenil-etil}-amida		1,47 (b)	518
276	Ácido (±)-(2-Cloro-4-{1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-carbámico metil éster		1,23 (b)	534

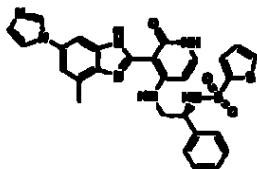
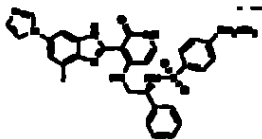
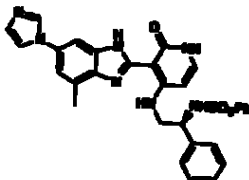
292

277	(±)-4-[1-Hidroximetil-2-(2-hidroxi-3-metil-fenil)etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 29 (b)	471
278	(S)-4-[2-(5-Bromo-2-metoxi-fenil)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 48 (b)	549
279	4-(2S-hidroxi-1-indan-1-il-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 42 (b)	467
280	(±)-4-[2-(3-Bromo-4-metil-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 43 (b)	519

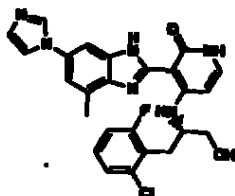
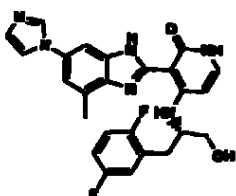
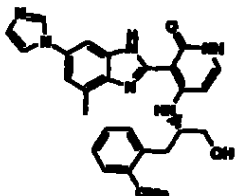
293

281	3-(6-Imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[2-(1H-indol-5-il)-etilamino]-1H-piridin-2-ona		1,54 (b)	450
282	Ácido (S)-3-(5-Bromo-2-metoxi-fenil)-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2oxo-1,2-dihidro-piridin-4-ilamino]-propiónico		1,09 (b)	563
283	Ácido (S)-Propano-2-sulfónico {2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-1-fenil-etil)-amida		1,34 (b)	532

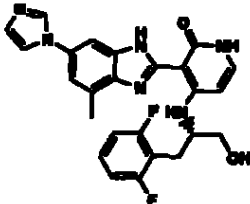
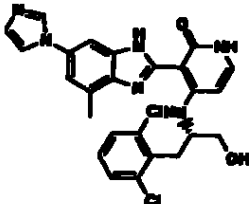
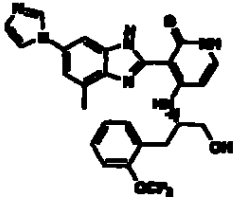
267
294

284	Ácido (S)-Tiofeno-2-sulfónico {2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-1-fenil-etil}-amida		2, 45(a)	572
285	(S)-N-{2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-1-fenil-etil}-4-metanosulfonilbencenosulfonamida		1, 34(b)	644
286	(S)-N-{2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidropiridin-4-ilamino]-1-fenil-etil}-bencenosulfonamida		1, 60(b)	566

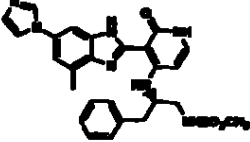
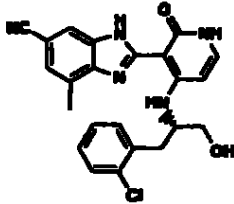
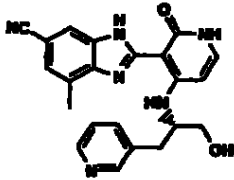
~~267~~
296

290	(S)-4-[2-(2-Cloro-6-fluoro-fenil)-1-hidroxi metil-etilamino]-3-(6-imidazol-1-il)-4-metil-1H-benzimidazol-2-il-1H-piridin-2-ona		1,40(a)	493
291	(S)-4-[2-(2,5-Difluoro-fenil)-1-hidroxi metil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,44(a)	477
292	(S)-4-[1-Hidroxi metil-2-(2-metoxi-fenilo)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,52(f)	471

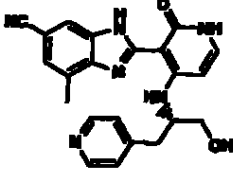
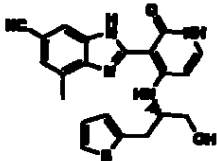
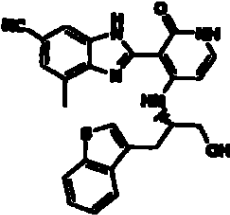
297

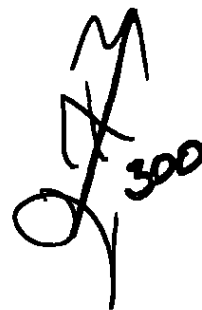
293	(S)-4-[2-(2,6-Difluorofenilo)-1-hidroxi metil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,42(a)	477
294	(S)-4-[2-(2,6-Difluorofenilo)-1-hidroxi metil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,42(a)	509
295	(S)-4-[1-Hidroxi metil-2-(2-trifluorometoxifenilo)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,48(a)	525

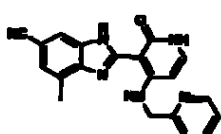
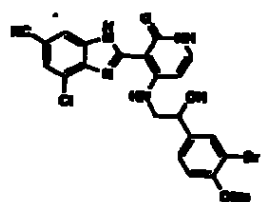
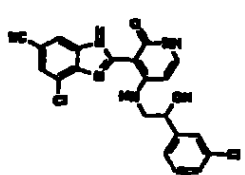
17
298

296	(s)-n-(2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4 ilamino]-3-fenil-propil)-metanesulfonamida.		1,31(a)	518
297	(S)-2-(4-[2-(2-Clorofenilo)-1-hidroximetil-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo.		1,80(b)	434
298	(S)-2-[4-(1Hidroximetil-2-piridin-3-il-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carbonitrilo.		1,07(b)	401

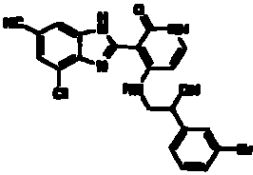
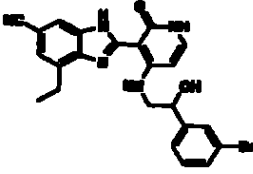
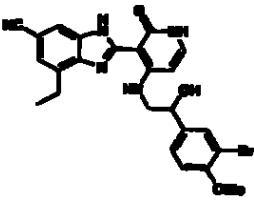
299

299	(S)-2-[4-(1-hidroxi-2-etilamino-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo.		1,15(b)	401
300	(S)-2-[4-(1-hidroxi-2-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carbonitrilo.		1,73(b)	406
301	(S)-2-[4-(2-benzo[b]tiofen-3-il-1-hidroxi-2-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carbonitrilo		1,84(b)	456

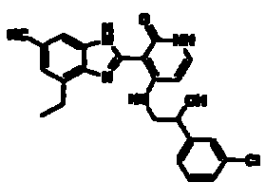
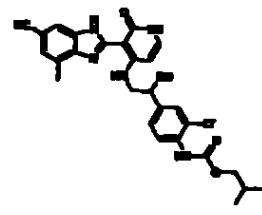
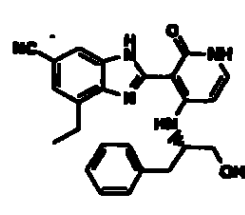


302	7-metil-2-{2-oxo-4- [(piridin-2-ilmetilo)- amino]-1,2-dihidro- piridin-3-il-3H- benzimidazol-5- carbonitrilo		1,30(b)	357
303	(±)-2-{4-[2-(3-Bromo- 4- metoxo-fenilo)-2- hidroxi-etilamino]-2- oxo-1,2-dihidro- piridin-3-il]-7-Cloro- 3H-benzimidazol-5- carbonitrilo		1,74(d)	514
304	(±)-2-{4-[2-(3-Cloro- fenilo)-2-hidroxi- etilamino]-2-oxo-1,2- dihidro-piridin-3-il]- 7-Cloro-3H- benzimidazol-5- carbonitrilo		1,78(d)	440

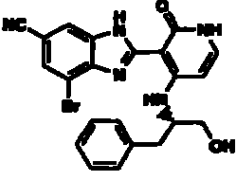
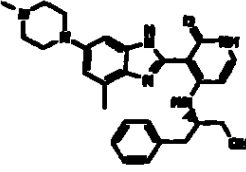
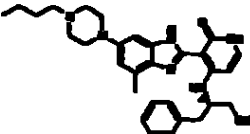
301

305	(±)-2-(4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il]-7-Cloro-3H-benzimidazol-5-carbonitrilo		1,77 (d)	484
306	(±)-2-(4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il]-7-etil-3H-benzimidazol-5-carbonitrilo		1,82 (d)	478
307	(±)-2-(4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il]-7-etil-3H-benzimidazol-5-carbonitrilo		1,76 (d)	508

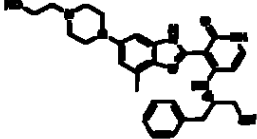
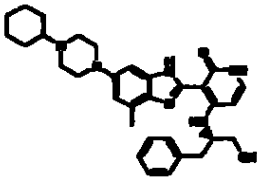
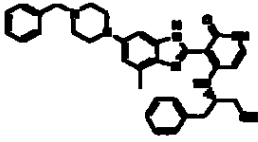
302

308	(±)-2-(4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-etil-3H-benzimidazol-5-carbonitrilo		1,80 (d)	434
309	Isobutil éster de ácido (±)-(2-Cloro-4-(2-[3-(6-ciano-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-1-hidroxi-etil)-fenilo)-carbámico		1,93 (b)	535
310	(S)-7-Bromo-2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-3H-benzimidazol-5-carbotilo		1,75 (d)	414

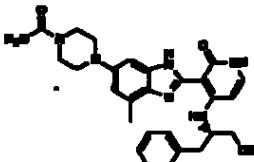
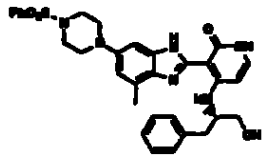
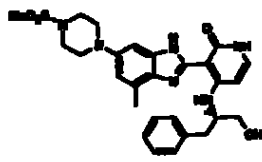
27/303

311	(S)-7-Bromo-2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-3H-benzimidazol-5-carbotilo		1,91(b)	464
312	(S)-4-[1-Hidroximetil-2-fenil-etilamino]-3-[4-metil-6-(4-metil-piperazin-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,08(f)	473
313	(S)-4-[1-Hidroximetil-2-fenil-etilamino]-3-[4-metil-6-(4-n-butil-piperazin-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,29(k)	515

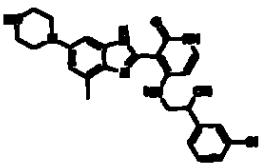
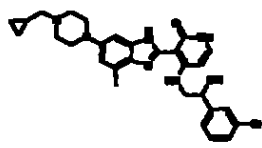
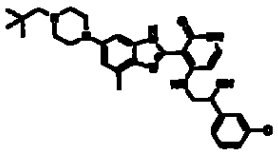
277
304

314	(S)-3-{6-[4-(2-Hidroxi-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il]}-4-(1-hiroximetil-2-fenil-etilamino)-1H-piridin-2-ona		1, 62 (k)	503
315	(S)-3-{6-[4-Ciclohexil-piperazin-1-il]-4-metil-1H-benzimidazol-2-il]-4-(1-hiroximetil-2-fenil-etilamino)-1H-piridin-2-ona		1, 34 (f)	541
316	(S)-3-[6-(4-benzil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenilo-etilamino)-1H-piridin-2-ona		1, 93 (f)	549

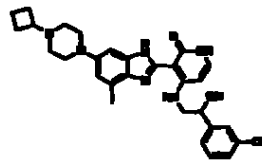
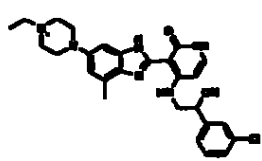
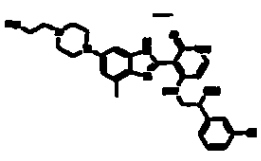
305

317	Ácido (S)-4-(2-[4-(1-Hidroximetil-2-fenilo-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico-amida.		1,26(f)	502
318	(S)-3-[6-(4-benzenesulfonylpiperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenilo-etilamino)-1H-piridin-2-ona		2,30(k)	599
319	(S)-4-[1-Hidroximetil-2-fenil-etilamino]-3-[6-(4-metanesulfonylpiperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,93(k)	537

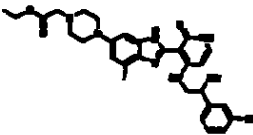
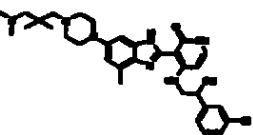
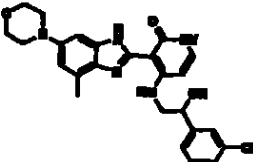
306

320	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6 piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,90 (f)	479
321	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6 piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,97 (k)	533
322	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2,2-dimetil-propil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona		2,06 (k)	549

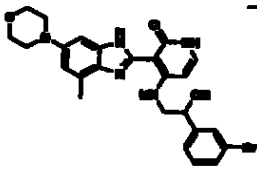
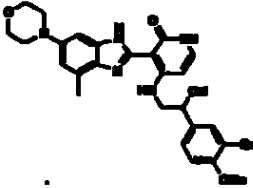
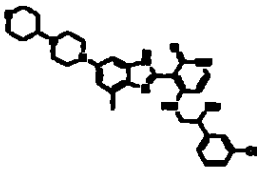


323	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[6-(4-ciclobutil piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,97 (k)	533
324	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[6-(4-etil piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,88 (k)	507
325	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[6-[4-(2-hidroxi-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,82 (k)	524

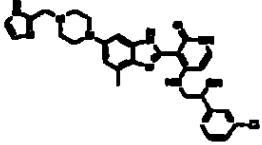
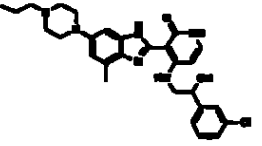
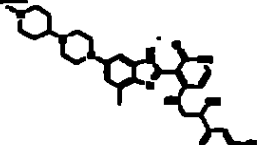
27
308

326	Etil éster de ácido (±)-[4-(2-{4-[2-(3- Cloro-fenilo)-2- hidroxi-etilamino]-2- oxo-1,2-dihidro- piridin-3-il} -7- metil-3H-benzimidazol- 5-il)-piperazin-1-il]- acético		2,03(k)	565
327	(±)-4-[2-(3-Cloro- fenilo)-2-hidroxi- etilamino]-3-{6-[4-(3- dimetilamino-2,2- dimetil-propil)- piperazin-1-il]-4- metil-1H-benzimidazol- 2-il}-1H-piridin-2-ona		1,84(k)	592
328	(±)-4-[2-(3-Cloro- fenilo)-2-hidroxi- etilamino]-3-(4-metil- 6-morfolin-4-il-1H- benzimidazol-2-il)-1H- piridin-2-ona		1,19(a)	480

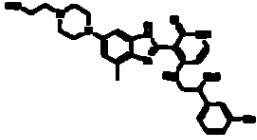
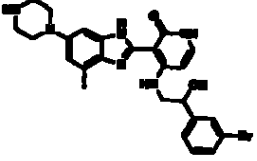
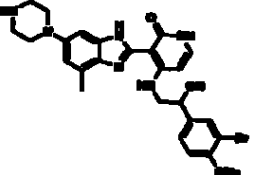
309

329	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,21(a)	524
330	(±)-4-[2-(3-Bromo-metoxi-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,16(a)	554
331	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-[4-(3-dimetilamino-2,2-dimetil-propil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,19(f)	563

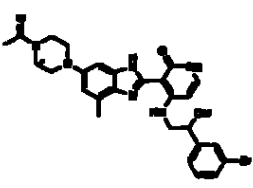
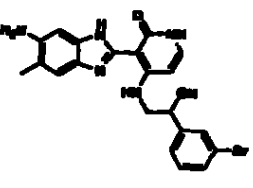
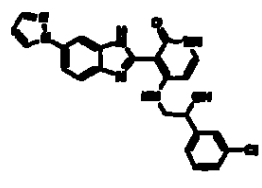
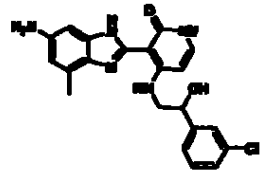
310

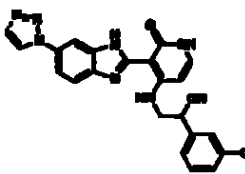
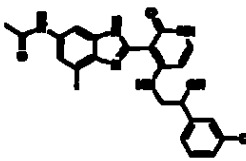
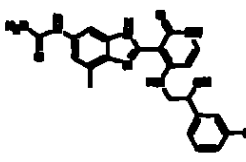
332	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[6-(4-imidazol-2-ilmetil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,19(f)	559
333	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(4-propil-piperazin-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,19(f)	521
334	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-[4-(1 metil-piperadin-4-il)-piperazin-1-il]-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,08(f)	576

311

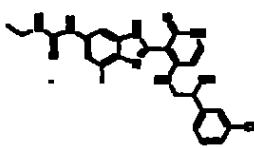
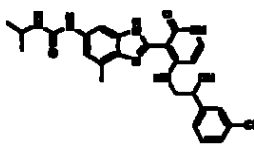
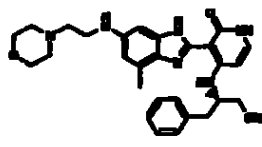
335	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-hidrixi-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,79 (f)	567
336	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,83 (f)	523
337	(±)-4-[2-(3-Bromo-4-metoksi-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,72 (f)	553

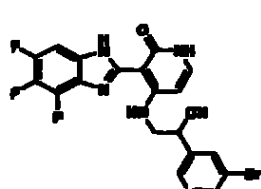
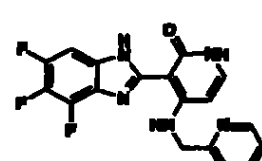
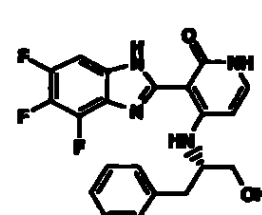
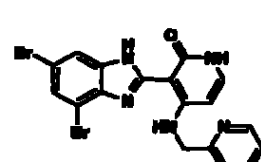
312

338	(±)-3-[6-(4-Acetil-piperzin-1-il)-4-metil-1H-benzimidazol-2-il]-4-[2-(3-bromofenil)-2-hidroxi-etilamino]-1H-piridin-2-ona		1,90(f)	565
339	(±)-3-(6-Amino-5-metil-1H-benzimidazol-2-il)-4-[2-(3-bromofenil)-2-hidroxi-etilamino]-1H-piridin-2-ona		1,14(j)	454
340	(±)-4-[2-(3-Clorofenilo)-2-hidroxi-etilamino]-3-(6-pirazol-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,86(f)	447
341	(±)-3-(6-Amino-4-metil-1H-benzimidazol-2-il)-4-[2-(3-clorofenil)-2-hidroxi-etilamino]-1H-piridin-2-ona		1,51(f)	410

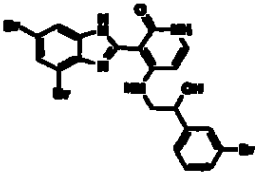
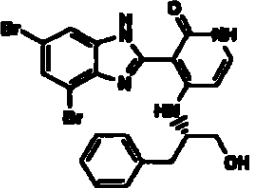
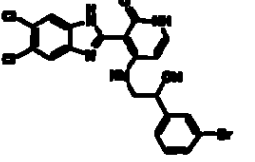
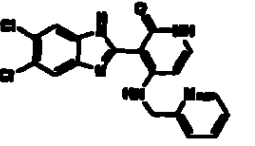
342	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-[1,2,3] triazol-1-il)-1H-benzimidazol-2-il)-1H-piridin-2-ona		2,04 (f)	448
343	(±)-N-(2-(4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidropiridin-3-il)-7-metil-3H-benzimidazol-5-il)-acetamida		1,62 (f)	452
344	(±)-(2-(4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidropiridin-3-il)-7-metil-3H-benzimidazol-5-il)-urea		1,49 (f)	453

314

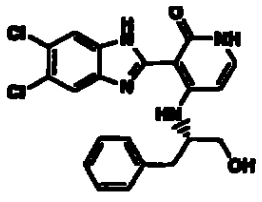
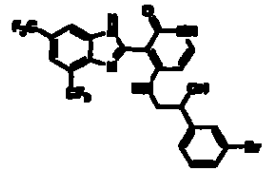
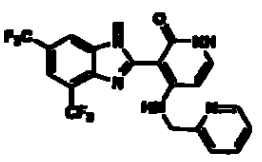
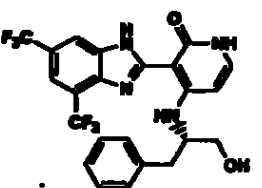
345	(±)-1-(2-(4-(2-(3-Cloro-fenilo)-2-hidroxi-etilamino)-2-oxo-1,2-dihidropiridin-3-il)-7-metil-3H-benzimidazol-5-il)-3-etil-urea		1,64(f)	481
346	(±)-1-(2-(4-(2-(3-Cloro-fenilo)-2-hidroxi-etilamino)-2-oxo-1,2-dihidropiridin-3-il)-7-metil-3H-benzimidazol-5-il)-3-isopropil-urea		1,71(f)	495
347	(S)-4-[1-Hidroximetil-2-fenil-etilamino)-3-[4-metil-6-(2-morfolin-4-il-etilamino)-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,05(f)	503

348	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(4,5,6-trifluoro-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,76(d)	479
349	4-[(piridin-2-ilmetil)amino]-3-(4,5,6-trifluoro-1H-benzimidazol-2-il)-1H-piridin-2-one		1,36(d)	372
350	(S)-4-(1-Hidroximetil-2-fenil-etilamino)-3-[4,5,6-trifluoro-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,73(d)	415
351	3-(4,6-Dibromo-1H-benzimidazol-2-il)-4-[(piridin-2-ilmetil)-amino]-1H-piridin-2-ona		1,66(d)	474

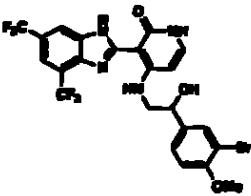
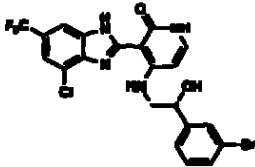
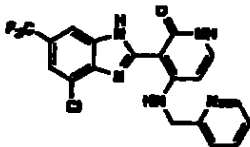
2316

352	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(4,6-dibromo-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,95 (d)	581
353	(S)-3-(4,6-Dibromo-1H-benzimidazol-2-il)-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona		1,92 (d)	517
354	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(5,6-dicloro-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,85 (d)	493
355	3-(5,6-Dicloro-1H-benzimidazol-2-il)-4-[(piridin-2-ilmetil) amino]-1H-piridin-2-ona		1,48 (d)	386

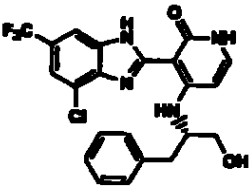
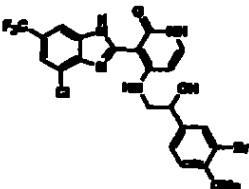
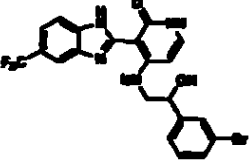
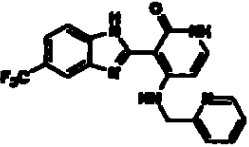
29
3A

356	(S)-3-(5,6-Dicloro-1H-benzimidazol-2-il)-4-(1-hidroximetil-2-fenilo-etilamino)-1H-piridin-2-ona		1,82(d)	429
357	(±)-3-(4,6-Bis-trifluorometil-1H-benzimidazol-2-il)-4-[2-(3-bromo-fenilo)-2-hidroxi-etilamino]1H-piridin-2-ona		1,56(b)	561
358	3-(4,6-Bis-trifluorometil-1H-benzimidazol-2-il)-4-[(piridin-2-ilmetil)-amino]1H-piridin-2-ona		1,39(b)	454
359	(S)-3-(4,6-Bis-trifluorometil-1H-benzimidazol-2-il)-4-(1-hidroximetil-2-fenil-etilamino)1H-piridin-2-ona		1,53(b)	497

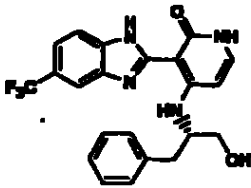
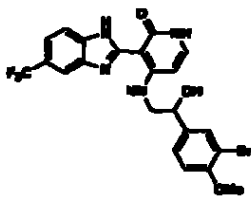
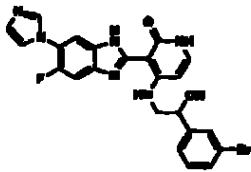
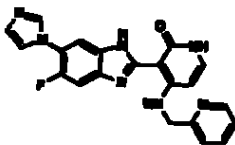
2318

360	(±)-3-(4,6-Bis-trifluorometil-1H-benzimidazol-2-il)-4-[2-(3-bromo-4-metoxifenil)-2-hidroxi-etilamino]1H-piridin-2-ona		1,51(b)	591
361	(±)-4-[2-(3-Bromofenilo)-2-hidroxi-etilamino]-3-(4-cloro-6-trifluorometil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,54(b)	527
362	3-(4-Cloro-6-trifluorometil-1H-benzimidazol-2-il)-4-[(piridin-2-ilmetil)amino]-1H-piridin-2-ona		1,34(b)	420

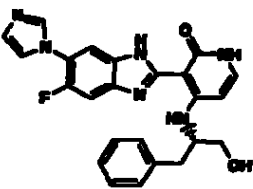
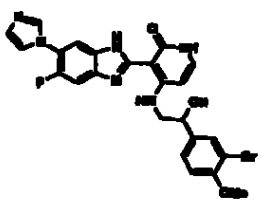
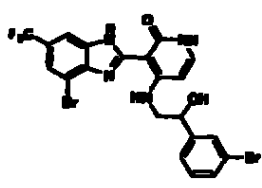
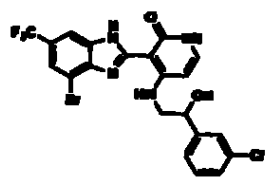
292
319

363	(±)-3-(4-Cloro-6-trifluorometil-1H-benzimidazol-2-il)-4-(1-hidroximetil-2-fenil-etilamino)1H-piridin-2-ona		1, 51 (b)	463
364	(±)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-(4-cloro-6-trifluorometil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 50 (b)	557
365	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(5-trifluorometil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 42 (b)	493
366	4-[(piridin-2-ilmetil)-amino]-3-(5-trifluorometil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 16 (b)	386

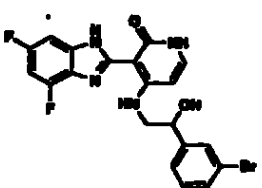
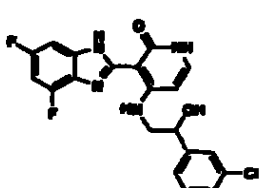
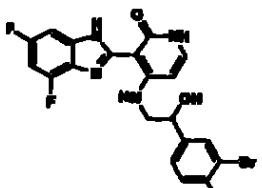
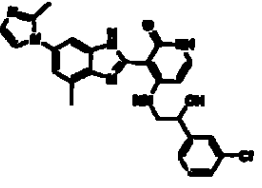
320

367	(S)-4-(1-hidroximetil-2-fenil-etilamino)-3-(5-trifluorometil-1H-benzimidazol-2-il)-1H-piridin-2-ona.		1, 41 (b)	429
368	(±)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-(5-trifluorometil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 38 (b)	523
369	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(5-fluoro-6-imidazol-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1, 10 (b)	509
370	3-(5-fluoro-6-imidazol-1-il-1H-benzimidazol-2-il)-4--[(piridin-2-ilmetil)-amino]-1H-piridin-2-ona		0, 73 (b)	402

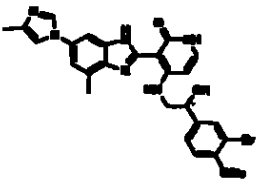
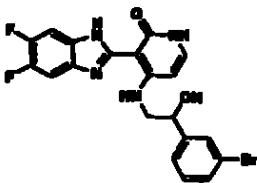
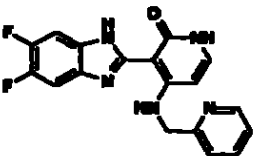
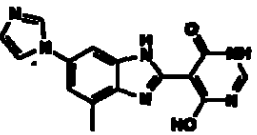
244
321

371	(S)-3-(5-fluoro-6-imidazol-1-il-1H-benzimidazol-2-il)-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona		1,04 (b)	445
372	(±)-4-[2-(3-Bromometoxi-fenilo)-2-hidroxi-etilamino]-3-(5-fluoro-6-imidazol-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,05 (b)	539
373	(±)-3-(4-Bromo-6-trifluorometil-1H-benzimidazol-2-il)-4-[2-(3-cloro-fenilo)-2-hidroxi-etilamino]1H-piridin-2-ona		1,97 (d)	571
374	(±)-3-(4-Bromo-6-trifluorometil-1H-benzimidazol-2-il)-4-[2-(3-bromo-fenilo)-2-hidroxi-etilamino]1H-piridin-2-ona		1,95 (d)	527

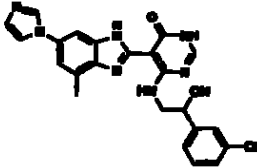
322

375	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(4,6-difluoro-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,72 (d)	461
376	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4,6-difluoro-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,70 (d)	417
377	(±)-4-[2-(3-Bromo-metoxi-fenilo)-2-hidroxi-etilamino]-3-(4,6-difluoro-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,65 (d)	491
378	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(2-metil-imidazol-1-il)-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,38 (d)	475

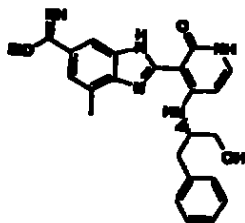
4/10
323

379	(±)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-(4-metil-imidazol-1-il)-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,35(d)	549
380	(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-[5,6-difluoro-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,67(b)	461
381	3-(5,6-Difluoro-1H-benzimidazol-2-il)-4-[(piridin-2-il-metil)-amino]-1H-piridin-2-ona		1,18(b)	354
382	6-Hidroxi-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-3H-pirimidin-4-one		0,96(f)	309

324

383	(±)-6-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		2,30 (f)	462
-----	--	--	----------	-----

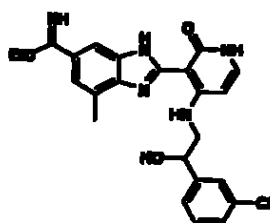
Formación de Imidato Intermedio (Esquema IV, 13)



Etil éster de (S)-2-[4-(1-Hidroximetil-2-fenilo-etilamino)-2-oxo-1,2-dihidro-piradin-3-il]-7-metil-3H-benzimidazol-5-carboximidico: A una suspensión de (S)-2-[4-(1-Hidroximetil-2-fenilo-etilamino)-2-oxo-1,2-dihidro-piradin-3-il]-7-metil-3H-benzimidazol-5-carbonitrilo (0,8 g, 2,0 mmoles) en etanol (anhidro, 80 ml) se burbujeó HCl (anhidro) a 0° C hasta saturación. La mezcla se convirtió en una solución clara después de pocos minutos de burbujeo y la solución se agitó a temperatura ambiente

225

durante 14 horas. Después de concentración in vacuo, el producto crudo (0.89 g, 100%) se utilizó directamente para el siguiente paso sin purificación. LCMS (M+H)⁺ m/z 446 (t=1,55 min).



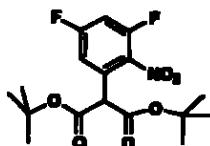
Etil éster de (±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-carboximidico: El procedimiento del título se preparó utilizando el procedimiento general. LCMS (M+H)⁺ m/z 466 (t=1,43 min).

Procedimiento general para los ejemplos 384-397 -
Formación de imidazolina (Esquema IV, 14).

326

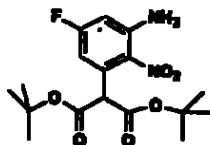
para producir el compuesto del título (180 mg, 55%). LCMS (M+H)⁺ m/z 344 (t= 1,31 min.)

Procedimiento para la preparación de 2-amina-4-fluor-6-metil nitrobenzeno:



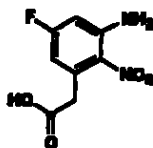
di-tert-butil ester de ácido 2-(3,5-difluor -2-nitro-fenil)-malónico: A una suspensión de NaH (54,6 g, 60%, 1,365 mol) en 600 ml de DMF se agregó di-t-butil malonato (118 g, 0,546 mol) a 0° C y se agitó durante 30 min. 2,4,6 trifluoronitrobenzeno se agregó como una solución en 400 ml de DMF (75 g, 0,42 mol) durante 3 horas y la solución se agotó a temperatura ambiente durante 12 horas. La mezcla de reacción se extrajo con etil acetato (3X). El etil acetato se lavó con agua (3X) y con agua salobre y se secó sobre MgSO₄ y se concentró para dar 62 g del producto crudo. LCMS [M+Na]-396;

¹H NMR (500MHz, DMSO) δ 7.81 (m, 1H), 7.27 (m, 1H), 5.00 (s, 1H), 1.41 (m, 18H).



di-tert-butyl ester de ácido 2-(3-amino-5-fluoro-2-nitro-fenil)-malónico: A di-tert-butyl ester de ácido 2-(3,5-difluoro-2-nitro-fenil)-malónico crudo (62 g , 0,42 mol) se agregó 70 ml de amonio 2 M y metano en una botella de presión. El vaso se selló y se calentó en 85° C durante 18 horas. La mezcla de reacción se enfrió y el vaso se abrió cuidadosamente y la solución de metano se concentró para suministrar 140 g de material crudo. LCMS [M+Na]-393;

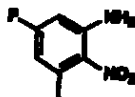
¹H NMR (500MHz, DMSO) δ 6.76 (dd, J=10.8 2.8Hz, 1H), 6.29 (dd, J=10.8, 2.8Hz, 1H), 4.99 (brs, 2H), 4.80 (s, 1H), 1.40 (m, 18H).



328

ácido 3-amino-5-fluor-2-nitro fenil acético: Al di-tert-butil éster de ácido 2(3-amino-5-floro-2-nitro-fenil)-malónico (140 g) en 500 ml de HCL 4N en dioxano se agregó 50 ml de agua y se calentó a 40° C durante 2 días. La solución se extrajo con acetato de etilo (3X) y el Acetato de etilo se lavó con agua (3X) y agua salobre. La fracción orgánica se secó sobre MgSO₄ y se concentró para dar 78 g de crudo (66% puro por LC/MS);

¹H NMR (500MHz, DMSO) δ 12.40 (brs, 1H), 7.04 (s, 2H), 6.68 (dd, J=10.9 2.8Hz, 1H), 6.47 (dd, J=10.9, 2.8Hz, 1H), 3.80 (s, 2H).



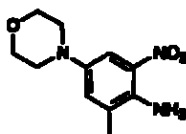
2-amino-4-floro-6-metil nitrobenceno: Al ácido 3-amino-5-fluoro-2-nitro fenil acético crudo (3,6 g, 16, 8 mmol) se agregó Cu₂O (10,1 g, 70, 6 mmol) en 120 ml de acetonitrilo junto con 50 ul de metanol y la suspensión se reflujo durante 12 horas. La mezcla de reacción se filtró a través de celita y la almohadilla de celita se lavó con agua y acetato de etilo. El filtrado se extrajo con acetato de etilo, se lavó con agua y agua solubre, se secó sobre Na₂SO₄ y se concentró para dar 2,95 g del

2
329

material el cual por medio de ^1H RMN fue 80% puro. ESIMS
[M+Na]-193;

^1H NMR (500MHz,
DMSO) δ 6.67 (s, 2H), 6.56 (dd, $J=11$, 2.8Hz, 1H), 6.39 (dd, $J=11$, 2.8Hz, 1H), 2.50
(s, 3H).

Procedimiento para la preparación de 4-cloro-3-(4-metil-6-morfolin-4-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona y 4-yodo-3-(4-metil-6-morfolin-4-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona.



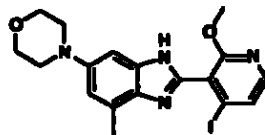
2-metil-4-morfolin-4-il-6-nitro-fenilamino: A un recipiente de presión de 800 ml se agregó tris (dibenzilidenoacetona) dipaladio (2,64 g, 2,88 mmol), 2-(Di-t-butilfosfino)bifenil (1,42 g, 4,75 mmol) y tert butoxido de sodio (17,5 g, 182 mmol) luego THF seco (500 ml), 4-bromo-2-metil-6-nitroanilina (30,0 g, 130 mmol) y morfolino (34 ml, 390 mmol) se agregaron. El argón se burbujeo a través de la solución durante 1 minuto y el recipiente se selló. La mezcla de reacción se agitó a 85°C durante 3 días. THF se evaporó in vacuo y el

330

producto crudo se preabsorbió sobre sílica y este luego se transfirió sobre la parte superior de la columna de sílica gel. La elusión con hexano-acetato de etilo (6:4 a 4:6 a 0:1 de gradientes) dio, después de la evaporación de los solventes, el compuesto del título (15,2 g de un sólido café rojo-café, 49,3%).

LCMS (M+H)⁺ m/z 238

(t = 0.64 min.) ¹H NMR (500 MHz, DMSO-d₆) δ 7.32 (1H, s), 7.22 (1H, s), 6.96 (2H, s), 3.72 (4H, Amp s), 2.96 (4H, Amp s), 2.21 (3H, s).

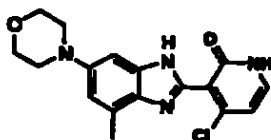


2-(4-yodo-2-metoxipiridin-3-il)-4-metil-6-morfolin-4-il-1H-benzoimidazol: 2-metil-4-morfolin-4-il-6-nitro-fenilamina (15,2 g, 64 mmol) se suspendieron en metanol (200 ml) en un recipiente PARR. Se agregó paladio sobre carbono (1,0 g, 10% Pd) y la suspensión se agitó bajo 60 psi de hidrogeno durante toda la noche. La mezcla se filtró a través de una almohadilla de Celita (bajo argón) en un recipiente de 3 cuellos, la celita se enjuagó con metanol y el filtrado se diluyó con metanol a un volumen total de 500 ml y se enfrió a 0°C. Una solución de 4-

331

yodo-2-metoxi-piridino-3-carbaldehído (14,6 g, 55,5 mmol) en metanol (500 ml) se agregó lentamente (durante 3 horas). Después de la adición de ~ ¼ de la solución el sistema se abrió al aire y se agitó durante el fin de semana, alcanzando de esta manera la temperatura ambiente. La mezcla de reacción se concentró in vacuo, se filtró a través de una almohadilla de sílica (eluente: metilenocloruro-acetato de etilo-metanol 55-40-5) luego se cristalizó de acetato de etilo. El compuesto del título se aisló como un sólido café (12,68 g, 51%). La cromatografía de columna d destello del licor madre (dio 2,90 g, adicionales 12%). [la columna de empaque con cloruro de metileno, compuesto eluido con cloruro de metileno-acetato de etilo 6-4, luego metilenocloruro-acetato de etilo-metanol 58-40-2].

LCMS (M+H)⁺ m/z 451 (t = 1.03 min.). ¹H NMR (500 MHz, CDCl₃) δ 7.76 (1H, d, J = 5.3 Hz), 7.42 (1H, d, J = 5.3 Hz), 6.85 (1H, Amp s), 6.82 (1H, s), 3.86 (4H, t, J = 4.5 Hz), 3.79 (3H, s), 3.12 (4H, t, J = 4.5 Hz), 2.60 (3H, s), 2.21 (3H, s).



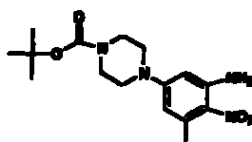
V
B
N
332

4-cloro-3-(4-metil-6-morfolin-4-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona y 4-yodo-3-(4-metil-6-morfolin-4-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona:

2-(4-yodo-2-metoxi-piridin-3-il)-4-metil-6-morfolin-4-il-1H-benzoimidazol (15,58 g, 34,6 mmol) se suspendió en 1,4-dioxano (300 ml) y HCl con (50 ml) se agregó. La mezcla se agitó a temperatura ambiente durante toda la noche, luego 3 horas 50°C. La mezcla se enfrió a temperatura ambiente y se vertió en hielo solución fría de NaHCO₃ (67 g, 0,8 mol) y se filtró. La fase acuosa se extrajo con acetato de etilo. El material sólido se disolvió en CH₂Cl₂ con algo de metanol, luego se extrajo entre agua y CH₂Cl₂. Las capas orgánicas combinadas fueron secadas sobre Na₂SO₄. y se concentró in vacuo para dar una mezcla inseparable de los compuestos del título 4-cloro y 4-yodo. El producto se utilizó sin purificación adicional LCMS (M+H)⁺ m/z 437 y m/z 345 (ambos t= 0,92 min.)

Procedimiento para la preparación de tert-butil éster de ácido 4-[2-(4-cloro-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il]-piperazina-1-carboxílico y tert-butil éster de ácido 4-[2-4-yodo-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il]-piperazina-1-carboxílico.

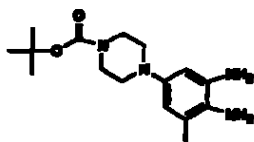
333



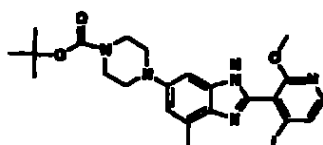
Tert-butil éster de ácido 4-(3-amino-5-metil-4-nitro-fenil)-piperazina-1-carboxílico: A una solución agitada de 3-floro-5-amino-6-nitrotolueno (10 g, 58,79 mmol) en NMP anhidro (160 ml) bajo nitrógeno se agregó BOC-piperazina (39 g, 209,4 mmol) y 4-metilmorfolino (25,9 ml). La solución oscura resultante se calentó a reflujo durante 72 h, se enfrió a temperatura ambiente y se diluyó con acetato de etilo (4000 ml). La capa orgánica se lavó con agua (8 x 1500 ml) agua salobre (1 x 1500 ml), se secó sobre sulfato de sodio y se evaporó in vacuo. El aceite oscuro resultante se disolvió en etanol absoluto hirviente (800 ml) y se concentró a un volumen total de 400 ml y se dejó que permaneciera durante toda la noche a temperatura ambiente. La solución se enfrió adicionalmente a -20°C durante 5 h y el sólido resultante se filtró y se secó i vacuo para dar 16,3 g (83%) de un sólido amarillo claro.

¹H NMR (500 MHz, CDCl₃) δ 6.16 (brs, 1H), 6.04 (brs, 1H), 3.70 – 3.60 (m, 4H), 3.38 – 3.25 (m, 4H), 2.53 (s, 3H), 1.48 (s, 9H); LCMS (M+H)⁺ m/z 337.

334



Tert-butil éster de ácido 4-(3,4-diamino-5-metil-fenil)-piperazina -1-carboxílico: A una solución agitada de tert-butil éster de ácido 4-(3-amino-5-metil-4-nitro-fenil)-piperazina-1-carboxílico (15 g, 44,6 mmol) en metanol (2200 ml) se agregó 20% de Pd (OH)₂/C (1,6 g) y la suspensión fluyó bien con nitrógeno, seguida por hidrógeno. La suspensión resultante se agitó durante toda la noche a temperatura ambiente bajo una atmósfera de hidrógeno (ca. 1 atm). La suspensión resultante se filtró bajo nitrógeno a través de una almohadilla de celita y se lavó con metanol (400-500 ml). El material resultante se utilizó inmediatamente. LCMS (M+H)⁺ m/z 307.

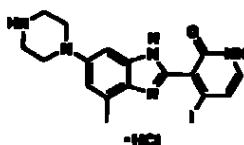


Tert-butil éster de ácido 4-[2-(4-yodo-2-metoxi-piridin-3-il)-7-metil-3H-benzoimidazol-5-il]-piperazina-1-carboxílico: A una solución agitada de 3-butil éster de ácido 4-(3,4-diamino-5-metil-fenil)-piperazina-1-carboxílico (44,6 mmol-asumiendo el 100% de conversión

338

(en la etapa previa) en metanol (ca 2700 ml) a 0°C bajo una atmósfera de nitrógeno se agregó lentamente (2 h) por vía de un embudo adicional, una solución de 4-yodo-2-metoxi-piridina-3-carbaldehído (15,0 g, 57,1 mmol) en metanol anhidro (225 ml). La solución resultante fue entonces agitada a 0°C durante 30 minutos adicionales, el baño enfriante se removió, y la mezcla de reacción se permitió agitarse a temperatura ambiente en la presencia de aire durante 72 horas. La solución resultante se concentró in vacuo y el residuo se disolvió en diclorometano (1500 ml) y el solvente se removió in vacuo (repitió 3x). El sólido espumoso oscuro resultante se secó bajo alto vacío.

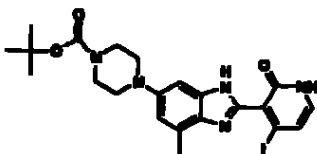
¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, 1H, J = 5.4 Hz), 7.50 (d, 1H, J = 5.4 Hz), 6.98 (brs, 1H), 6.90 (brs, 1H), 4.05 (s, 3H), 3.67 – 3.58 (m, 4H), 3.18 – 3.09 (m, 4H), 2.63 (s, 3H), 1.49 (s, 9H); LCMS (M+H)⁺ m/z 550.



4-yodo-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona: A una solución agitada de 3-butil éster de ácido 4-[2-(4-yodo-2-metoxi-piridin-3-il)-7-

229
336

metil-3H-benzoimidazol-5-il]-piperazina-1-carboxílico (24 g, 43,7 mmol) se agregó a 1,4-dioxano (750 ml) y HCl acuoso 6 N (30 ml) y la mezcla se calentó a 75°C durante la noche. La solución se enfrió a temperatura ambiente, el supernadante se vertió, y el sólido gomoso oscuro resultante se enfrió se lavó con dietil eter anhidro (3 x 500 ml) y se secó in vacuo para dar 17,7 g (93%) del título del compuesto como un sólido oscuro que fue utilizado como se despidió para preparar tert-butil éster de ácido 4-[2-(4-cloro-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il]-piperazina-1-carboxílico y tert-butil éster de ácido 4-(2-(4-yodo-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il)piperazina-1-carboxílico; LCMS (M+H)⁺ m/z 436. (nota: un pico pequeño (4-cloro-piridin-2-ona) en LC/MS mostró m/z 344,346).



tert-butil éster de ácido 4-[2-(4-cloro-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il]-piperazina-1-carboxílico y tert-butil éster de ácido 4-[2-(4-yodo-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-

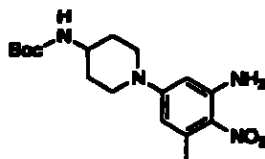
337

benzoimidazol-5-il]-piperazina-1-carboxílico: A una suspensión agitada de 4-yodo-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona (17,7 g, 40, 7 mmol) en diclorometano (750 ml) se agregó di-tert-butil bicarbonato (9,8 g, 44,8 mmol) y trietilamina (67,4 ml, 483,6 mmol). La mezcla se agitó a temperatura ambiente durante 30 min. Y se purificó por vía de cromatografía de destello sobre sílica gel. Después de elusión con diclorometano seguido por 2,5% de metanol/etil acetato, se combinaron las fracciones homogéneas y se evaporó parcialmente in vacuo para dar el producto como un sólido amarillo, siguiendo filtración (8,9 g, ca 41%, 2 cultivos).

¹H NMR (500 MHz, CD₃OD) δ 7.25 (d, 1H, J = 6.9 Hz), 6.97 (d, 1H, J = 6.9 Hz), 6.97 (brs, 1H), 6.89 (brs, 1H), 3.65 – 3.56 (m, 4H), 3.16 – 3.07 (m, 4H), 2.55 (s, 3H), 1.49 (s, 9H); LCMS (M+H)⁺ m/z 536.
(Nota: un pico pequeño (4-cloro-piridin-2-ona) en LC/MS mostró m/z 444, 446).

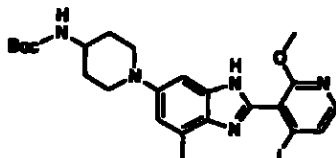
Procedimiento para la preparación de 3-[6-(4-amino-piperidin-1-il)-4-metil-1H-benzoimidazol-2-il]-4-yodo-1H-piridin-2-ona y 3-[6-(4-amino-pipridin-1-il)-4-metil-1H-benzoimidazol-2-il]-4-cloro-1H-piridin-2-ona.

338



Tert-butil éster de ácido 1-(3-amino-5-metil-4-nitro-fenil)-piperidin-4-il]-carbámico: 5-fluoro-3-metil-2-nitro-fenilamina (0,97 g, 5,7 mmol), 4-N-BOC-aminopiperidina (1,60 g, 8,0 mmol) diisopropiletilamina (2,5 ml, 14 mmol) y DMSO (10 ml) se combinaron y agitaron a 85°C durante 3 horas. La mezcla de reacción se vertió sobre una solución de NaHCO₃ acuoso saturado y se extrajo con etil acetato. Las capas orgánicas fueron lavadas con agua (3x) y agua salobre, se secaron sobre Na₂SO₄ y se concentraron. La cromatografía de columna de destello sobre sílica (eluente hexano-etil acetato-trietilamina 50-50-1, entonces 33-66-1) dio el compuesto del título como un sólido amarillo. (1,57 g, 79%).

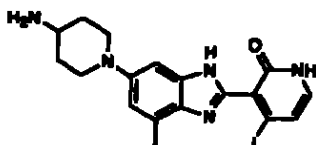
LCMS (M+H)⁺ m/z 351 (t = 1.55 min.). ¹H NMR (500 MHz, CD₃OD) δ 6.70 (1H, Amp s), 6.22 (1H, d, J = 2.5 Hz), 6.13 (1H, d, J = 2.5 Hz), 3.88 (2H, d, J = 13.3 Hz), 3.58 (1H, Amp s), 2.98 (2H, t, J = 11.8 Hz), 2.48 (3H, s), 1.92 (2H, d, J = 11.3 Hz), 1.48 (2H, m), 1.45 (9H, s).



332
339

Tert-butil éster de ácido (1-[2-(4-yodo-2-metoxi-piridin-3-il)-7-metil-3H-benzoimidazol-5-il]-piperidin-4-il)-

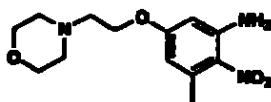
carbamico: Tert-butil éster de ácido [1-(3-amino-5-metil-4-nitro-fenil)-piperidin-4-il]-carbamico (1,54 g, 4,4 mmol) se disolvió en metanol (100 ml). Se agregó paladio sobre carbono (0,3 g, 10% Pd) y la suspensión se agitó vigorosamente bajo una presión de balón de hidrógeno durante toda la noche. La mezcla se filtró a través de una almohadilla de celita (bajo argón) en un frasco de 3 cuellos, la celita se enjuagó con metanol y el filtrado se enfrió a 0°C. Una solución de 4-yodo-2-metoxi-piridina-3-carbaldehído (1,21 g, 4,6 mmol) en metanol (50 ml) se agregó lentamente (durante 2 horas). La mezcla fue agitada durante toda la noche bajo aire a temperatura ambiente, luego se concentró in vacuo. La cromatografía de columna de destello sobre sílica (eluyente hexanos-etil acetato-metanol 5-4-1- dio el compuesto del título. (0,79 g, 32%). LCMS (M+H)⁺ m/z 564 (t = 1,31 min).



3-[6-(4-amino-piperidin-1-il)-4-metil-1H-benzoimidazol-2-il]-4-yodo-1H-piridin-2-ona y 3-[6-(4-amino-piperidin-1-il)-4-metil-1H-benzoimidazol-2-il]-4-cloro-1H-piridin-2-

340

ona: tert-butil éster de ácido (1-[2-(4-yodo-2-metoxipiridin-3-il)-7-metil-3H-benzoimidazol-5-il]-piperidin-4-il)-carbámico (330 mg, 0,59 mmol) se suspendieron en HCl 4M en 1,4-dioxano (20 ml) y agua (3 ml) se agregaron. (Reacción exotérmica) la mezcla se agitó a temperatura ambiente durante toda la noche, luego se concentró in vacuo para dar una mezcla inseparable de los compuestos del título 4-cloro y 4-yodo. El producto se utilizó sin purificación adicional. LCMS (M+H)⁺ m/z 450 y m/z 358 (ambos t=0,69 min.).

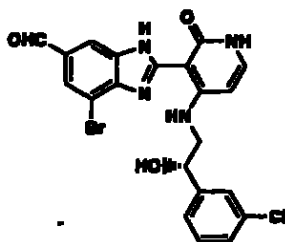


3-metil-5-(2-morfolin-4-etoxi)-2-nitro-fenilamino: A una solución de 2-morfolin-4-il-etanol (5 g, exceso) en THF (3° ml) se agregó NaH (0,21 G, 8,82 mol) en porción bajo baño de hielo. La mezcla de reacción se agitó a temperatura ambiente durante 30 min. Luego se agregó 5-fluoro-3-metil-2-nitro-fenilamina. La mezcla de reacción se calentó a reflujo durante 6 h, se enfrió a temperatura ambiente, y se concentró. El residuo se diluyó con agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua, agua salobre, y se secaron sobre Na₂SO₄. Después de la concentración, el residuo se purificó

341

mediante cromatografía de columna (20% de EtOAc /hexano) para producir el compuesto de título (0,70g, 85%).

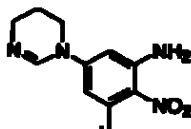
^1H NMR (400 MHz, CD_3OD) δ 6.10 (1H, s), 6.09 (1H, s), 4.38 – 4.42 (2H, m), 3.92 – 4.08 (4H, m), 3.72 (1H, d, $J = 12$ Hz), 3.53 – 3.56 (2H, m), 3.05 – 3.10 (2H, m), 2.48 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 282 ($t = 0.73$ min.).



(S)-7-bromo-2-{4-[2-(3-cloro-fenil)2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-3H-benzimidazol-5-carbaldehído: A una solución de (S)-7-bromo-2-{4-[2-(3-cloro-fenil)2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-3H-benzimidazol-5-carbonitrilo (150 mg, 0,31 mmol) en THF (50 ml) se agregaron DIBAL-H (solución de tolueno 1M, 1,55 ml, 1,55 mmol) a -78°C . La mezcla de reacción se agitó a -40°C durante 10 horas y se enfrió a -78°C . EtOAc (0,5 ml) se agregó. La mezcla de reacción se agitó durante 30 min a -78°C antes de que se agregara agua (1 ml). La mezcla de reacción se calentó a temperatura ambiente y se concentró. El residuo se paso a través de una pequeña almohadilla de celita. El filtrado se concentró y se purificó mediante HPLC prep. Para dar el compuesto del título (67 mg, 43%).

342

¹H NMR (400 MHz, CD₃OD) δ 9.45 (1H, s), 7.62 (1H, s), 7.56 (1H, Ang d, J = 1.6 Hz), 7.44 (1H, Ang d, J = 1.0 Hz), 7.32 - 7.42 (2H, m), 7.24 - 7.30 (3H, m), 6.24 (1H, d, J = 7.6 Hz), 5.01 (1H, m), 3.65 - 3.76 (2H, m). LCMS (M+H)⁺ m/z 487 (t = 1.76 min.).

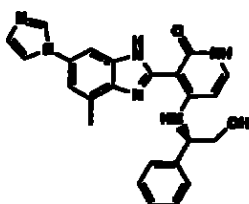


5-(1,4,5,6-tetrahydropyrimidin-1-il)-3-metil-2-nitro anilina: A una solución agitada de 2,0 g (11,76 mmol) de 5-fluoro-3-metil-2-nitro anilina en 10 ml de DMSO se agregó 1,2 g (14,11 mmol) 1,4,5,6-tetrahydropirimidina, y 2,43 g (17,64 mmol) de carbonato de potasio, y la mezcla se calentó a 100°C durante 10 horas, se enfrió, se diluyó con agua y se extrajo con etil acetato que contenía 5% de metanol. El extracto orgánico combinado se levó con agua, agua salobre y se secó (Na₂SO₄). La evaporación del solvente adecuó el residuo, el cual fue cromatografiado (20% de amonio 2M en metanol y diclorometano) para producir 1,85 g (67%) del producto como un sólido rojo.

343

¹H NMR (400 MHz, CD₃OD) δ 7.89 (1H, s), 6.53 (1H, d, *J* = 2.57 Hz), 6.44 ((1H, d, *J* = 2.1 Hz), 7.04 (1H, d, *J* = 2.1 Hz), 3.70 (2H, t, *J* = 6.0 Hz), 3.41 (2H, t, *J* = 5.65 Hz), 2.43 (3H, s), 2.05 (2H, m) LCMS (M+H)⁺ *m/z* 235 (*t* = 0.78 min).

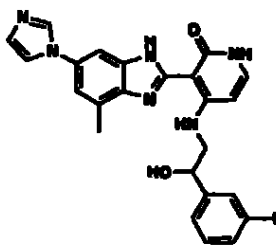
Ejemplo 1 (procedimiento general para los ejemplos 1-21).



(S)-4-(-2-hidroxi-1-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1h-benzimidazol-2-il)-1h-piridin-2-ona: a una solución de 3-(6-imidazol-1-il-4-metil-1h-benzimidazol-2-il)-4-yodo-1h-piridin-2-ona (30 mg, 0,072 mmol) en DMF (1 ml) se agregó (s) -(-)-2-fenilglicinol (26 mg, 0,18 mmol) y N-metilmorfolino (0,1 ml). La mezcla de reacción se calentó a 80°C durante 6 h y se enfrió a temperatura ambiente. El solvente se removió bajo vacío y el residuo se purificó mediante HPL prep. Para producir el compuesto del título, (16 mg, 52%).

¹H NMR (300 MHz, CD₃OD) δ 8.07 (1H, narrow t, *J* = 1.7 Hz), 7.76 (2H, s), 7.27 – 7.48 (7H, m), 7.21 (1H, d, *J* = 7.5 Hz), 6.11 (1H, d, *J* = 7.5 Hz), 4.92 (1H, m), 4.03 (1H, dd, *J* = 4.5, 11.2 Hz), 3.95 (1H, dd, *J* = 6.2, 11.2 Hz), 2.75 (3H, s). LCMS (M+H)⁺ *m/z* 427 (*t* = 1.44 min.)

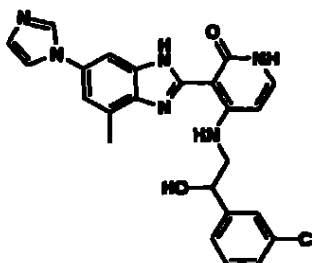
Ejemplo 2



(±)-4-[-2-hidroxi-2-(3-yodo-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 9.41 (1H, s), 8.06 (1H, s), 7.88 (1H, s), 7.76 (1H, s), 7.71 (1H, s), 7.59 (1H, d, *J* = 7.8 Hz), 7.47 (1H, d, *J* = 7.8 Hz), 7.32 (1H, s), 7.29 (1H, d, *J* = 7.6 Hz), 7.09 (1H, t, *J* = 7.8 Hz), 6.24 (1H, d, *J* = 7.6 Hz), 4.97 (1H, dd, *J* = 5.0, 6.0 Hz), 3.75 (1H, dd, *J* = 5.0, 13.5 Hz), 3.67 (1H, dd, *J* = 6.0, 13.5 Hz), 2.68 (3H, s). LCMS (M+H)⁺ *m/z* 553 (*t* = 1.43 min.).

Ejemplo 3



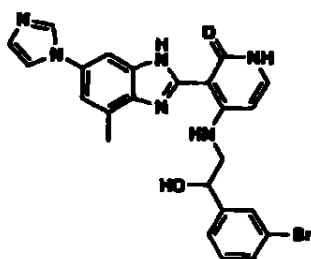
345

(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 9.39

(1H, Ang t, J = 1.4 Hz), 8.04 (1H, Ang t, J = 1.7 Hz), 7.76 (1H, Ang t, J = 1.7 Hz), 7.69 (1H, Ang d, J = 1.9 Hz), 7.55 (1H, s), 7.23 – 7.42 (5H, m), 6.25 (1H, d, J = 7.6 Hz), 5.01 (1H, dd, J = 4.8, 6.4 Hz), 3.76 (1H, dd, J = 4.8, 13.4 Hz), 3.66 (1H, dd, J = 6.4, 13.4 Hz), 2.67 (3H, s). LCMS (M+H)⁺ m/z 461 (t = 1.46 min.).

Ejemplo 4



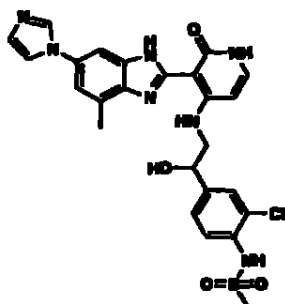
(±)-4-[2-(3-bromo-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 9.38

(1H, s), 8.02 (1H, s), 7.74 (1H, s), 7.69 (1H, s), 7.66 (1H, Ang d, J = 1.4 Hz), 7.20 – 7.48 (5H, m), 6.21 (1H, d, J = 7.6 Hz), 4.99 (1H, dd, J = 4.8, 6.3 Hz), 3.73 (1H, dd, J = 4.8, 13.5 Hz), 3.64 (1H, dd, J = 6.3, 13.5 Hz), 2.65 (3H, s). LCMS (M+H)⁺ m/z 505 (t = 1.47 min.).



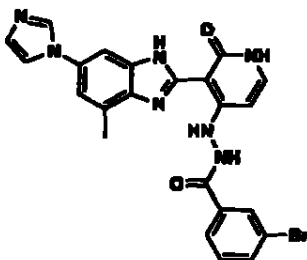
Ejemplo 5



(±)-N-(2-cloro-4-{1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil}-fenil)-metanosulfonamida:

¹H NMR (300 MHz, CD₃OD) δ 9.39 (1H, s), 8.05 (1H, s), 7.76 (1H, s), 7.68 (1H, s), 7.62 (1H, ^{Ang} d, J = 1.5 Hz), 7.52 (1H, s), 7.42 – 7.49 (2H, m), 7.31 (1H, s), 7.30 (1H, d, J = 7.6 Hz), 6.26 (1H, d, J = 7.6 Hz), 5.01 (1H, dd, J = 5.0, 5.6 Hz), 3.76 (1H, d, J = 5.0, 13.4 Hz), 3.74 (1H, dd, J = 5.6, 13.4 Hz), 2.98 (3H, s), 2.68 (3H, s). LCMS (M+H)⁺ m/z 554 (t = 1.11 min.).

Ejemplo 6

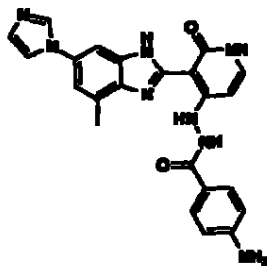


347

Acido 3-bromo-benzoico-N'-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-1-il)-2-oxo-1,2-dihidro-piridin-4-il]-hidrazida:

^1H NMR (300 MHz, CD_3OD) δ 9.40 (1H, Ang t, $J = 1.4$ Hz), 8.14 (1H, Ang t, $J = 1.7$ Hz), 8.05 (1H, Ang t, $J = 1.7$ Hz), 7.95 (1H, d, $J = 7.9$ Hz), 7.81 (1H, d, $J = 7.9$ Hz), 7.74 – 7.77 (2H, m), 7.49 (1H, t, $J = 7.9$ Hz), 7.41 (1H, d, $J = 7.4$ Hz), 7.34 (1H, s), 6.38 (1H, d, $J = 7.4$ Hz), 2.70 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 504 ($t = 1.44$ min.).

Ejemplo 7

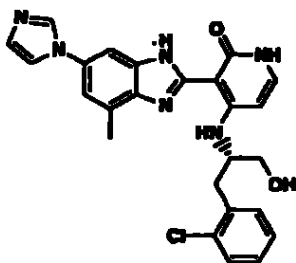


Acido 4-aminobenzoico N'-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-1-il)-2-oxo-1,2-dihidro-piridin-4-il]-hidrazida:

^1H NMR (300 MHz, CD_3OD) δ 9.41 (1H, s), 8.06 (1H, s), 7.76 – 7.79 (4H, m), 7.39 (1H, d, $J = 7.4$ Hz), 7.36 (1H, s), 6.81 (2H, d, $J = 8.6$ Hz), 6.36 (1H, d, $J = 7.4$ Hz), 2.70 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 441 ($t = 0.96$ min.).

37
348

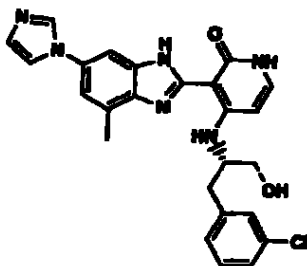
Ejemplo 8



(S)-4-[2-(2-cloro-fenil)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ
9.41 (1H, s), 8.05 (1H, ^{Ang}_{Ang} t, J = 1.7 Hz), 7.76 (1H, ^{Ang}_{Ang} t, J = 1.7 Hz), 7.72 (1H, ^{Ang}_{Ang} d, J = 1.9 Hz), 7.08 – 7.36 (6H, m), 6.10 (1H, d, J = 7.7 Hz), 3.98 – 4.24

Ejemplo 9



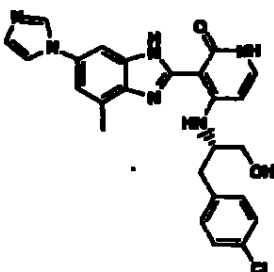
(S)-4-[2-(3-cloro-fenil)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

349

¹H NMR (300 MHz, CD₃OD) δ

9.42 (1H, s), 8.07 (1H, *Ang* t, *J* = 1.7 Hz), 7.75 – 7.78 (2H, m), 7.14 – 7.37 (6H, m), 6.18 (1H, d, *J* = 7.7 Hz), 4.07 – 4.11 (1H, m), 3.76 – 3.77 (2H, m), 3.17 (1H, dd, *J* = 5.1, 13.7 Hz), 2.98 (1H, dd, *J* = 8.2, 13.7 Hz), 2.71 (3H, s). LCMS (M+H)⁺ *m/z* 475 (*t* = 1.57 min.).

Ejemplo 10



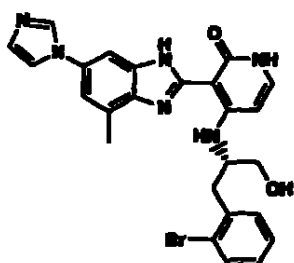
(S)-4-[2-(4-cloro-fenil)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ

9.42 (1H, s), 8.07 (1H, *Ang* t, *J* = 1.6 Hz), 7.77 (1H, *Ang* t, *J* = 1.6 Hz), 7.73 (1H, *Ang* d, *J* = 1.9 Hz), 7.16 – 7.37 (6H, m), 6.19 (1H, d, *J* = 7.7 Hz), 4.06 – 4.10 (1H, m), 3.72 – 3.77 (2H, m), 3.14 (1H, dd, *J* = 5.3, 13.8 Hz), 2.98 (1H, dd, *J* = 7.8, 13.8 Hz), 2.69 (3H, s). LCMS (M+H)⁺ *m/z* 475 (*t* = 1.61 min.).

Ejemplo 11

978
350

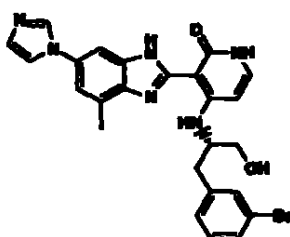


(S)-4-[2-(2-bromo-fenil)-1-hidroxi-metil-etil-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ

9.41 (1H, s), 8.06 (1H, s), 7.75 – 7.77 (2H, m), 7.52 (1H, dd, *J* = 1.5, 7.5 Hz), 7.36 (1H, d, *J* = 1.9 Hz), 7.34 (1H, s), 7.03 – 7.16 (3H, m), 6.09 (1H, d, *J* = 7.7 Hz), 4.15 – 4.27 (1H, m), 3.82 (2H, m), 3.35 (1H, dd, *J* = 5.0, 13.6 Hz), 3.10 (1H, dd, *J* = 9.0, 13.6 Hz), 2.74 (3H, s). LCMS (M+H)⁺ *m/z* 519 (*t* = 1.56 min.).

Ejemplo 12



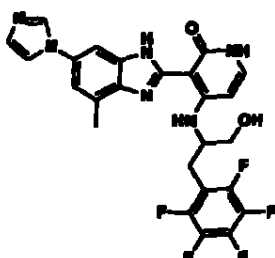
(S)-4-[2-(3-bromo-fenil)-1-hidroxi-metil-etil-amino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

351

¹H NMR (300 MHz, CD₃OD) δ

9.41 (1H, s), 8.06 (1H, s), 7.74 – 7.77 (2H, m), 7.47 (1H, s), 7.24 – 7.31 (4H, m), 7.11 (1H, d, *J* = 7.7 Hz), 6.16 (1H, d, *J* = 7.7 Hz), 4.05 – 4.11 (1H, m), 3.76 (2H, m), 3.15 (1H, dd, *J* = 5.0, 13.6 Hz), 2.96 (1H, dd, *J* = 8.3, 13.6 Hz), 2.70 (3H, s). LCMS (M+H)⁺ *m/z* 519 (*t* = 1.54 min.).

Ejemplo 13

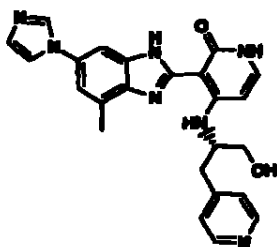


(±)-4-(1-hidroximetil-2-pentafluorofenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ

9.40 (1H, s), 8.06 (1H, Ang *t*, *J* = 1.8 Hz), 7.77 (1H, Ang *t*, *J* = 1.7 Hz), 7.74 (1H, Ang *d*, *J* = 1.8 Hz), 7.35 (1H, s), 7.29 (1H, d, *J* = 7.6 Hz), 6.22 (1H, d, *J* = 7.6 Hz), 4.24 (1H, m), 3.82 (2H, dd, *J* = 2.6, 4.5 Hz), 3.23 (2H, *t*, *J* = 6.5 Hz), 2.70 (3H, s). LCMS (M+H)⁺ *m/z* 531 (*t* = 1.61 min.).

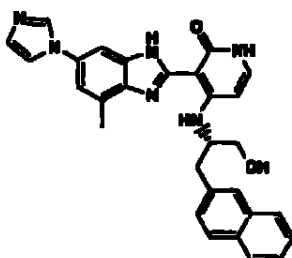
Ejemplo 14



(S)-4-(1-hidroximetil-2-piridin-4-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

^1H NMR (400 MHz, CD_3OD) δ 9.42 (1H, s), 8.67 (2H, d, $J = 6.6$ Hz), 8.07 (2H, d, $J = 6.6$ Hz), 8.06 (1H, s), 7.77 (2H, s), 7.36 (1H, s), 7.28 (1H, d, $J = 7.6$ Hz), 6.24 (1H, d, $J = 7.6$ Hz), 4.35 (1H, m), 3.82 (2H, d, $J = 4.4$ Hz), 3.50 (1H, dd, $J = 4.4, 13.6$ Hz), 3.40 (1H, dd, $J = 8.7, 13.6$ Hz), 2.71 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 442 ($t = 0.96$ min.).

Ejemplo 15



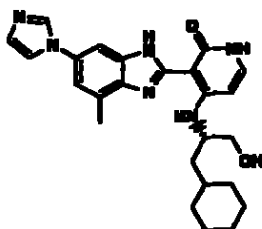
(S)-4-(1-hidroximetil-2-nafteleno-2-il-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

353

¹H NMR (300 MHz, CD₃OD) δ

7.99 (1H, *Ang* t, *J* = 1.7 Hz), 7.26 – 7.75 (11H, m), 7.15 (1H, d, *J* = 7.6 Hz), 6.19 (1H, d, *J* = 7.6 Hz), 4.16 – 4.20 (1H, m), 3.75 – 3.86 (2H, m), 3.30 (1H, dd, *J* = 5.4, 13.6 Hz), 3.15 (1H, dd, *J* = 7.6, 13.6 Hz), 2.60 (3H, s). LCMS (M+H)⁺ *m/z* 491 (*t* = 1.71 min.).

Ejemplo 16



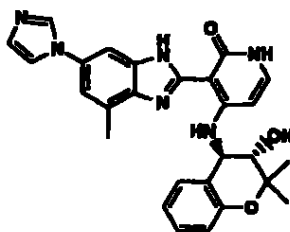
(S)-4-(2-ciclohexil-1-fenil)-1-hidroxi metil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 9.40

(1H, s), 8.06 (1H, *Ang* t, *J* = 1.7 Hz), 7.76 (1H, *Ang* t, *J* = 1.7 Hz), 7.73 (1H, *Ang* d, *J* = 1.7 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 7.33 (1H, s), 6.34 (1H, d, *J* = 7.6 Hz), 3.89 – 3.94 (1H, m), 3.68 (2H, d, *J* = 4.9 Hz), 2.68 (3H, s), 1.62 – 1.83 (7H, m), 0.95 – 1.26 (6H, m). LCMS (M+H)⁺ *m/z* 447 (*t* = 1.71 min.).

Ejemplo 17

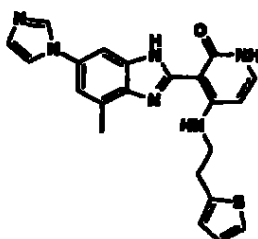
354



(3S,4R)-4-(3-hidroxi-2,2-dimetil-croman-4-ilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 9.36 (1H, s), 8.02 (1H, ¹Ang t, J = 1.7 Hz), 7.73 (1H, ¹Ang t, J = 1.7 Hz), 7.69 (1H, ¹Ang d, J = 2.0 Hz), 7.37 (1H, d, J = 7.6 Hz), 7.18 - 7.30 (3H, m), 6.89 (1H, t, J = 7.6 Hz), 6.85 (1H, d, J = 8.4 Hz), 6.61 (1H, d, J = 7.6 Hz), 4.93 (1H, d, J = 8.2 Hz), 3.80 (1H, d, J = 8.2 Hz), 2.46 (3H, s), 1.48 (3H, s), 1.35 (3H, s). LCMS (M+H)⁺ m/z 483 (t = 1.70 min.).

Ejemplo 18

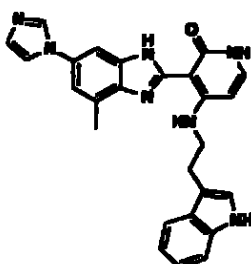


3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-(2-tiofen-2-il-etilamino)-1H-piridin-2-ona:

355

¹H NMR (500 MHz, DMSO-d₆) δ 13.17 (1H, s), 11.32 (1H, Amp s), 11.03 (1H, broad s), 9.59 (1H, Amp s), 8.22 (1H, l Amps), 7.91 (1H, s), 7.82 (1H, d, *J* = 2.0 Hz), 7.41 (1H, t, *J* = 6.9 Hz), 7.36 (1H, dd, *J* = 1.0, 5.1 Hz), 7.30 – 7.40 (1H, m), 7.05 (1H, broad s), 7.01 (1H, t, *J* = 4.2 Hz), 6.23 (1H, d, *J* = 7.5 Hz), 3.74 (2H, t, *J* = 6.5 Hz), 3.25 (2H, t, *J* = 6.5 Hz), 2.58 (3H, s).

Ejemplo 19

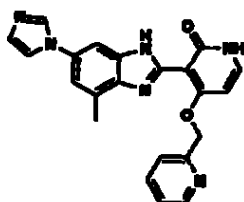


3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-[2-(1H-indol-3-il)-etilamino]-1H-piridin-2-ona:

¹H NMR (500 MHz, DMSO-d₆) δ 13.17 (1H, s), 11.27 (Amp s, 1H), 11.00 (1H, Amp s), 10.89 (1H, s), 9.58 (1H, Amp s), 8.30 (1H, Amp s), 7.91 (1H, s), 7.80 (1H, s), 7.63 (1H, d, *J* = 7.9 Hz), 7.40 (1H, t, *J* = 6.9 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.30 – 7.40 (2H, m), 7.07 (1H, t, *J* = 7.5 Hz), 6.99 (1H, t, *J* = 7.6 Hz), 6.23 (1H, dd, *J* = 0.8, 7.2 Hz), 3.76 (2H, Amp s), 3.17 (2H, t, *J* = 6.7 Hz), 2.50 (3H, s).

Ejemplo 20

356



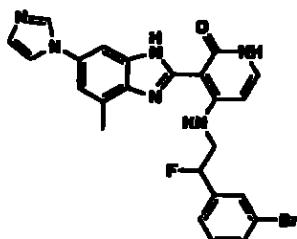
3-(6-imidazol-1-yl-4-metil-1H-benzimidazol-2-il)-4-

[piidin-2-ilmetoxi-1H-piridini-2-ona: A una solución de 3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-yodo-1H-piridin-2-ona (25 mg, 0,06 mmol) DMF (2 ml) se agregó piridina carbinol (26 mg, 0,24 mmol) y fluoruro de cesio (36 mg, 0,24 mmol). La mezcla de reacción se calentó a 130°C durante 14 h y se enfrió a temperatura ambiente. Después de concentración in vacuo, el residuo se purificó mediante HPLC prep. Para producir el compuesto del título (8,2 mg, 34%).

¹H NMR (300 MHz, CD₃OD) δ 9.58 (1H, Ang d, J = 1.2 Hz), 8.92 (1H, d, J = 4.9 Hz), 8.19 (1H, Ang t, J = 1.2 Hz), 8.12 (1H, s), 7.97 – 8.02 (2H, m), 7.85 (1H, Ang t, J = 1.8 Hz), 7.81 (1H, Ang t, J = 1.0 Hz), 7.63 (1H, d, J = 7.9 Hz), 7.54 (1H, t, J = 6.2 Hz), 6.81 (1H, J = 7.5 Hz), 5.86 (2H, s), 2.86 (3H, s). LCMS (M+H)⁺ m/z 399 (t = 1.07 min.).

Ejemplo 21

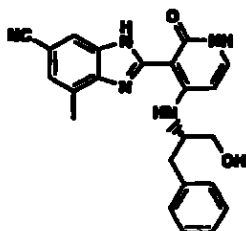
357



(±)-4-[-2-(3-bromo-fenil)-2-fluoro-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

^1H NMR (300 MHz, CD_3OD) δ 9.40 (1H, t, $J = 1.4$ Hz), 8.06 (1H, t, $J = 1.9$ Hz), 7.76 (1H, t, $J = 1.7$ Hz), 7.72 (1H, d, $J = 1.9$ Hz), 7.66 (1H, s), 7.27 – 7.50 (5H, m), 6.29 (1H, d, $J = 7.6$ Hz), 5.75 – 5.94 (1H, m), 3.86 – 4.06 (2H, m), 2.64 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 507 ($t = 1.70$ min.).

Ejemplo 22 (procedimiento general para los ejemplos 22 - 28)



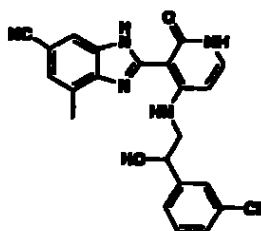
(S)-2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carbonitrilo: A una solución de 2-(4-cloro-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo (0,7 g, 2,19 mmol) en DMF (15 ml) se agregó N-metilmorfolino (0,66 g, 6,57 mmol) y (S)-(-)-2-amino-3-

23
358

fenil-1-propanol (0,40 g, 2,63 mmol) la mezcla de reacción se calentó a 80°C durante 6 h luego se enfrió a temperatura ambiente. Después de concentración in vacuo, el residuo se purificó mediante cromatografía de destello (3% MeOH/CH₂Cl₂) para producir el compuesto del título (0,59 g, 68%) como a una espuma amarilla.

¹H NMR (400 MHz, CD₃OD) δ 7.74 (1H, s), 7.63 (1H, s), 7.12 – 7.27 (6H, m), 6.07 (1H, d, *J* = 7.5 Hz), 3.97 (1H, m), 3.74 (2H, t, *J* = 5 Hz), 3.14 (1H, dd, *J* = 5.5, 14.0 Hz), 2.94 (1H, dd, *J* = 7.9, 14.0 Hz), 2.60 (3H, s). LCMS (M+H)⁺ *m/z* 400 (*t* = 1.71 min.).

Ejemplo 23

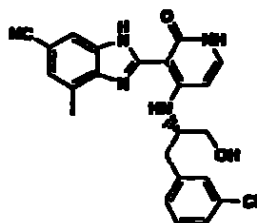


(±)-2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carbonitrilo:

¹H NMR (300 MHz, DMSO-d₆) δ 7.92 (1H, s), 7.59 (1H, s), 7.28 – 7.47 (5H, m), 6.19 (1H, d, *J* = 7.3 Hz), 4.92 – 4.96 (1H, m), 3.53 – 3.73 (2H, m), 2.58 (3H, s). LCMS (M+H)⁺ *m/z* 420 (*t* = 1.99 min.).

232
359

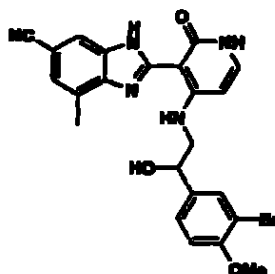
Ejemplo 24



(S)-2-(4-[2-(3-cloro-fenil)-1-hidroxi-metil-etil-amino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo:

^1H NMR (400 MHz, CD_3OD) δ 7.86 (1H, s), 7.10 – 7.33 (6H, m), 6.12 (1H, d, $J = 7.6$ Hz), 4.01 – 4.05 (1H, m), 3.75 (2H, d, $J = 4.9$ Hz), 3.15 (1H, dd, $J = 4.9, 13.5$ Hz), 2.86 – 3.00 (1H, m), 2.63 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 434 ($t = 1.81$ min.).

Ejemplo 25

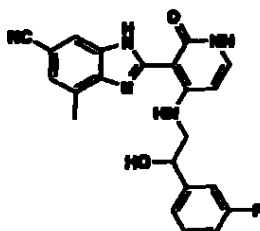


(±)-2-(4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-etil-amino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo:

360

¹H NMR (300 MHz, CD₃OD) δ 7.86 (1H, s), 7.75 (1H, s), 7.67 (1H, s), 7.28 – 7.40 (2H, m), 6.95 (1H, d, *J* = 8.5 Hz), 6.24 (1H, d, *J* = 7.4 Hz), 4.93 (1H, m), 3.65 – 3.97 (2H, m), 3.82 (3H, s), 2.57 (3H, s). LCMS (M+H)⁺ *m/z* 494 (*t* = 2.10 min.).

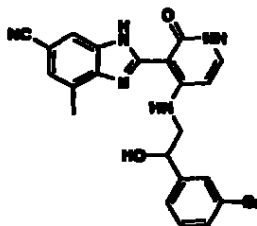
Ejemplo 26



(±)-2-(4-[2-(3-fluorophenyl)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo:

¹H NMR (400 MHz, CD₃OD) δ 7.70 (1H, s), 7.49 (1H, s), 7.22 – 7.32 (4H, m), 6.92 (1H, d, *J* = 8.9 Hz), 6.17 (1H, d, *J* = 7.2 Hz), 4.92 (1H, t, *J* = 6.3 Hz), 3.66 (2H, d, *J* = 5.9 Hz), 2.56 (3H, s). LCMS (M+H)⁺ *m/z* 404 (*t* = 1.65 min.).

Ejemplo 27

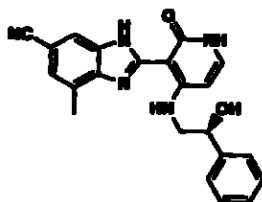


361

(±)-2-(4-[2-(3-bromo-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo:

¹H NMR (300 MHz, CD₃OD) δ 7.92 (1H, s), 7.72 (1H, s), 7.26 – 7.50 (5H, m), 6.19 (1H, d, J = 7.1 Hz), 4.93 (1H, t, J = 4.3 Hz), 3.47 – 3.73 (2H, m), 2.58 (3H, s). LCMS (M+H)⁺ m/z 464 (t = 2.00 min.).

Ejemplo 28



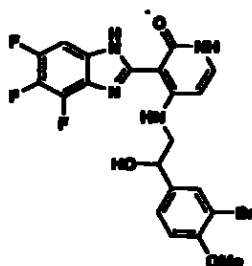
(S)-2-[4-(2-hidroxi-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carbonitrilo:

¹H NMR (400 MHz, CD₃OD) δ 8.04 (1H s), 7.74 (1H, s), 7.24 – 7.51 (6H, m), 6.22 (1H, d, J = 7.5 Hz), 5.00 (1H, m), 3.64 – 3.74 (2H, m), 2.60 (3H, s). LCMS (M+H)⁺ m/z 386 (t = 1.65 min.).

Ejemplo 29-35 Se prepararon de diaminas comercial o fácilmente disponibles que fueron preparadas y condensadas con 4-yodo-2-metoxi-piridina-3-carbaldehído como se describió en el esquema III.

362

Ejemplo 29

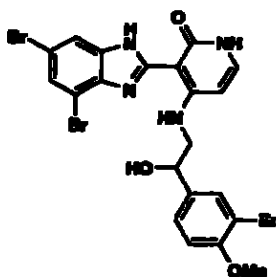


(±)-4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-3-(4,5,6-trifluoro-1H-benzimidazol-2-il)-1H-piridin-2-ona :

¹H NMR (500 MHz, CD₃COCD₃) δ

13.26 (1H, Amp s), 10.93 (1H, Amp s), 10.27 (1H, Amp s), 7.76 (1H, s), 7.54 – 7.56 (2H, m), 7.41 – 7.42 (1H, m), 7.06 (1H, d, J = 8.2 Hz), 6.29 (1H, d, J = 7.5 Hz), 5.05 – 5.07 (1H, m), 3.87 (3H, s), 3.74 – 3.79 (1H, m), 3.65 – 3.69 (1H, m).

Ejemplo 30



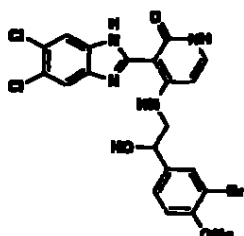
(±)-4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-metilamino]-3-(4,6-dibromo-1H-benzimidazol-2-il)-1H-piridin-2-ona:

363

¹H NMR (500 MHz, CD₃COCD₃) δ

13.18 (1H, Amp s), 11.18 (1H, Amp s), 10.20 (1H, Amp s), 7.92 (1H, s), 7.78 (1H, s), 7.52 – 7.55 (3H, m), 7.03 (1H, d, J = 8.5 Hz), 6.28 (1H, d, J = 7.4 Hz), 5.06 – 5.08 (1H, m), 3.86 (3H, s), 3.73 – 3.77 (1H, m), 3.66 – 3.70 (1H, m).

Ejemplo 31

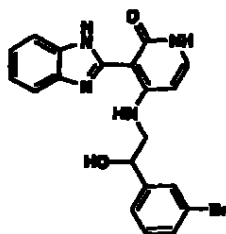


(±)-4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-metilamino]-
3-(5,6-dicloro-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (500 MHz, CD₃COCD₃) δ 7.79

(3H, m), 7.53 (1H, dd, J = 2.0, 8.4 Hz), 7.41 – 7.44 (1H, m), 7.08 (1H, d, J = 8.4 Hz), 6.29 (1H, d, J = 7.5 Hz), 5.05 – 5.08 (1H, m), 3.89 (3H, s), 3.74 – 3.78 (1H, m), 3.70 – 3.72 (1H, m).

Ejemplo 32

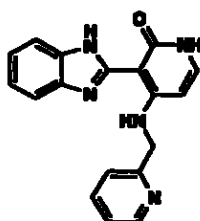


(±)-3-(1H-benzimidazol-2-il)-4-[2-(3-bromo-fenil)-2-
hidroxi-etilamino]-1H-piridin-2-ona:

364

^1H NMR (500 MHz, CD_3COCD_3) δ 7.80 (1H, s), 7.64 – 7.69 (2H, m), 7.60 (1H, d, $J = 7.7$ Hz), 7.46 – 7.48 (2H, m), 7.33 (1H, t, $J = 7.8$ Hz), 7.19 – 7.22 (2H, m), 6.59 (1H, d, $J = 4.5$ Hz), 5.12 – 5.14 (1H, m), 5.13 (1H, dd, $J = 4.5, 7.2$ Hz), 3.82 (1H, dd, $J = 4.5, 13.6$ Hz), 3.71 (1H, dd, $J = 7.2, 13.6$ Hz).

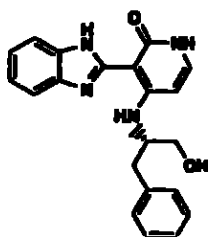
Ejemplo 33



3-(1H-benzimidazol-2-il)-4-[(piridin-2-ilmetil)-amino]-
1H-piridin-2-ono:

^1H
NMR (500 MHz, CD_3COCD_3) δ 8.96 – 8.98 (1H, m), 8.46 – 8.49 (1H, m), 8.03 (1H, d, $J = 8.0$ Hz), 7.93 (1H, t, $J = 6.4$ Hz), 7.69 – 7.73 (2H, m), 7.53 (1H, d, $J = 7.5$ Hz), 7.28 – 7.32 (2H, s), 6.34 (1H, d, $J = 7.5$ Hz), 5.29 (2H, m).

Ejemplo 34.

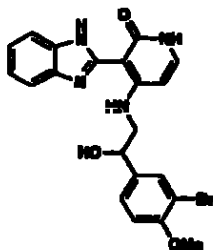


(S)-3-(1h-benzimidazol-2-il)-4-(1-hidroximetil-2-fenil-etilamina)-1H-piridin-2-ona:

^1H NMR (500 MHz, CD_3COCD_3) δ 7.67 – 7.69 (2H, m), 7.15 – 7.44 (8H, m), 6.31 (1H, d, $J = 7.5$ Hz), 4.10 – 4.13 (1H, m), 3.76 – 3.82 (2H, m), 3.23 (1H, dd, $J = 5.6, 13.7$ Hz), 3.04 (1H, dd, $J = 8.1, 13.7$ Hz).

27h
365

Ejemplo 35

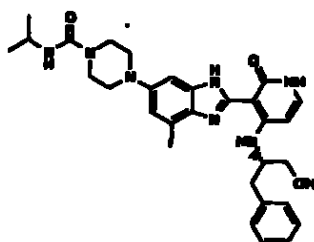


(±)-3-(1H-benzimidazol-2-il)-4-[2-(3-bromo-metoxi-fenil)-2-hidroxi-etilamino]-1H-piridin-2-ona:

^1H NMR (500 MHz, CD_3COCD_3) δ 7.78 (1H, s), 7.68 (2H, s), 7.50 – 7.55 (2H, m), 7.21 – 7.24 (2H, m), 7.06 (1H, d, $J = 8.4$ Hz), 6.44 (1H, d, $J = 7.5$ Hz), 5.08 (1H, dd, $J = 4.6, 7.2$ Hz), 3.87 (3H, s), 3.79 (1H, dd, $J = 4.6, 13.4$ Hz), 3.71 (1H, dd, $J = 7.2, 13.4$ Hz).

Ejemplo 36-43 Se prepararon de acuerdo con el esquema V.

Ejemplo 36 (procedimiento general para los ejemplos 36-43)



Isopropilamida de ácido (S)-4-{2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-il]-piperazina-1-carboxílico : A una

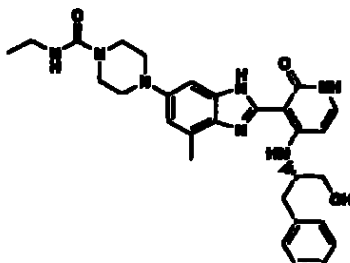
366

solución de (S)-4-(1-hidroximetil-2-fenil-etilamino)-3-(4-metil-6-piprazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona (30 mg, 0,63 mmol) en metanol (2 ml) se agregó isopropil isocianato (2 gotas). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos, la concentración dio el residuo, el cual se purificó mediante HPLC prep. Para producir el compuesto del título (23,8 mg, 69%).

¹H

NMR (400 MHz, CD₃OD) δ 7.55 (1H, s), 7.14 – 7.28 (7H, m), 6.12 (1H, d, J = 7.8 Hz), 4.01 – 4.03 (1H, m), 3.92 (quintet, J = 6.6 Hz), 3.80 (4H, m), 3.76 (1H, dd, J = 4.8, 11.2 Hz), 3.70 (1H, dd, J = 5.2, 11.2 Hz), 3.61 – 3.64 (4H, m), 3.09 (1H, dd, J = 5.6, 13.7 Hz), 2.91 (1H, dd, J = 8.0, 13.7 Hz), 2.64 (3H, s), 1.19 (6H, d, J = 6.8 Hz).
LCMS (M+H)⁺ m/z 545 (t = 1.99 min.).

Ejemplo 37



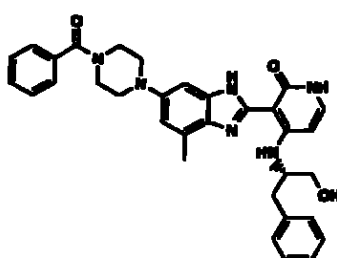
Etilamina de ácido (S)-4-(2-[4-(1-hidroximetil-2-fenil-etilamina)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3-benzimidazol-5-il)-piperazina-1-carboxílico:

367

¹H NMR

(400 MHz, CD₃OD) δ 7.55 (1H, s), 7.12 – 7.28 (7H, m), 6.12 (1H, d, *J* = 7.8 Hz), 4.01 – 4.05 (1H, m), 3.62 – 3.81 (10H, m), 3.24 (2H, q, *J* = 7.2 Hz), 3.08 (1H, dd, *J* = 5.6, 13.7 Hz), 2.91 (1H, dd, *J* = 8.0, 13.7 Hz), 2.65 (3H, s), 1.14 (3H, t, *J* = 7.2 Hz). LCMS (M+H)⁺ *m/z* 531 (*t* = 1.93 min.).

Ejemplo 38



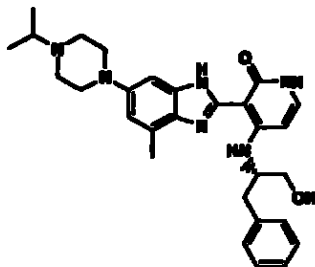
(S)-4-(1-hidroxiometil-2-fenil-etilamina)-3-{4-metil-6-[4-(1-fenil-metanoil-piperazin-1-il)]-1H-benzimidazol-2-il}-1H-piridin-2-ona. A una solución de (S)-4-(1-hidroxiometil-2-fenil-etilamino)-3-(4-metil-6-piperazin-1-il)-1H-benzimidazol-2-il)-1H-piridin-2-ona (30 mg, 0,063 mmol) en metanol (2 ml) se agregó benzoil cloruro (1 gota). La mezcla de reacción se agitó durante 5 minutos y se concentró. El residuo se purificó mediante HPLC prep. Para producir el compuesto del título (11 mg, 33%).

¹H

NMR (400 MHz, CD₃OD) δ 7.48 – 7.54 (5H, m), 7.37 (1H, s), 7.13 – 7.26 (7H, m), 6.08 (1H, d, *J* = 7.7 Hz), 3.79 – 4.02 (5H, m), 3.76 (1H, dd, *J* = 4.7, 11.2 Hz), 3.67 (1H, dd, *J* = 5.7, 11.2 Hz), 3.54 (4H, m), 3.03 (1H, dd, *J* = 5.7, 13.7 Hz), 2.89 (1H, dd, *J* = 8.0, 13.7 Hz), 2.62 (3H, s). LCMS (M+H)⁺ *m/z* 563 (*t* = 2.19 min.).

34
368

Ejemplo 39

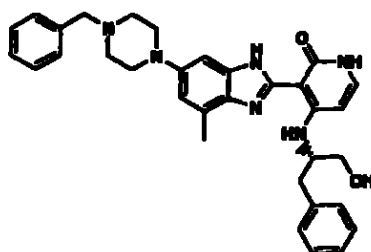


(S)-4-(1-hidroximetil-2-fenil-etilamino)-3-[6-(4-isopropil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona: A una solución de (S)-4-(1-hidroximetil-2-fenil-etilamino)-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona (25 mg, 0,054 mmol) en metanol (0,5 ml) se agregó acetona (0,25 ml) y una solución de THF 1 M de NaCNBH₃ (0,2 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 h se concentró in vacuo. El residuo se purificó mediante HPLC prep. Para producir el compuesto del título (12 mg, 44%).

¹H NMR (400 MHz, CD₃OD) δ 7.10 – 7.24 (6H, m), 7.08 (1H, s), 7.06 (1H, s), 6.06 (1H, d, J = 7.9 Hz), 3.58 – 4.01 (10H, m), 3.34 (1H, m), 3.14 (1H, m), 2.98 (1H, dd, J = 5.9, 13.7 Hz), 2.83 (1H, dd, J = 7.9, 13.7 Hz), 2.60 (3H, s), 1.44 (6H, d, J = 6.7 Hz). LCMS (M+H)⁺ m/z 501 (t = 1.80 min.).

Ejemplo 40

369

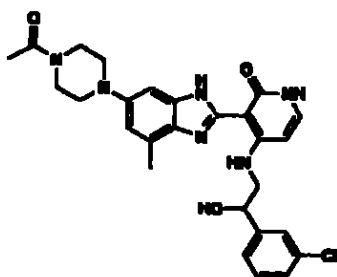


(S)-3-[6-(4-benzil-piperazina-1-il)-4-metil-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD)

δ 7.50 – 7.57 (6H, m), 7.04 – 7.27 (7H, m), 6.07 (1H, d, *J* = 7.8 Hz), 4.22 (2H, s), 3.97 – 4.00 (1H, m), 3.34 – 3.77 (2H, m), 2.82 – 3.04 (10H, m), 2.58 (3H, s). LCMS (*M*+*H*)⁺ *m/z* 549 (*t* = 1.93 min.).

Ejemplo 41

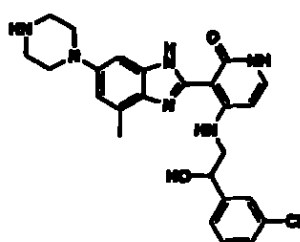


(±)-3-[6-(4-acetil-piperazina-1-il)-4-metil-1H-benzimidazol-2-il]-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-1H-piridin-2-ona:

370

¹H NMR (400 MHz, CD₃OD) δ 7.50 (1H, s), 7.25 – 7.49 (5H, m), 7.20 (1H, s), 6.25 (1H, d, *J* = 8.0 Hz), 4.94 (1H, dd, *J* = 4.6, 7.1 Hz), 3.88 – 3.92 (4H, m), 3.50 – 3.65 (6H, m), 2.62 (3H, s), 2.20 (3H, s). LCMS (M+H)⁺ *m/z* 521 (*t* = 2.13 min.).

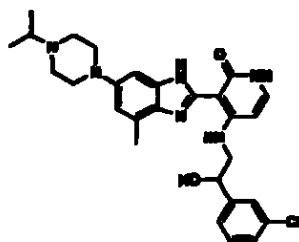
Ejemplo 42



(±)-4-[2-(3-cloro-fenil)-2-hidroxi-metilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.47 (1H, s), 7.25 – 7.38 (4H, m), 7.07 (2H, s), 6.25 (1H, d, *J* = 7.6 Hz), 4.90 (1H, m), 3.42 – 3.66 (10 H, m), 2.59 (3H, s). LCMS (M+H)⁺ *m/z* 479 (*t* = 1.90 min.).

Ejemplo 43.

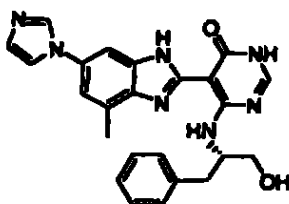


371

(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-[6-(4-isopropil-piperazina-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.47 (1H, s), 7.25 – 7.38 (4H, m), 7.06 (2H, s), 6.26 (1H, d, *J* = 7.6 Hz), 4.91 – 4.93 (1H, m), 3.89 – 3.92 (2H, m), 3.51 – 3.64 (5H, m), 3.31 – 3.37 (2H, m), 3.09 – 3.30 (2H, m), 2.59 (3H, s), 1.44 (6H, d, *J* = 6.6 Hz). LCMS (M+H)⁺ *m/z* 521 (*t* = 1.95 min.).

Ejemplo 44



(S)-6-(1-hidroximetil-2-fenil-etilamino)-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-3H-pirimidin-4-ona:

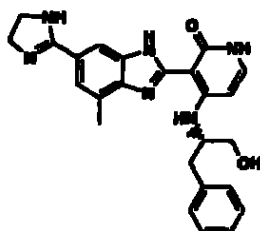
(S)-2-[6-cloro-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-pirimidin-4-ilamina]-3-fenil-propan-1-ol: A una solución de 2-4,6-dicloro-pirimidin-5-il)-6-imidazol-1-il-4-metil-1H-benzimidazol (40 mg, 0,16 mmol) en isopropanol (5 ml) se agregó (S)-(-)-2-AMINO-3-FENIL-propanol (35 mg, 0,23 mmol) y trietilamina (0,5 ml). La mezcla de reacción se calentó a 80°C durante 4 h se enfrió a temperatura ambiente y se concentró con vacío

alto. El producto crudo se utilizó para la siguiente etapa sin purificación. LCMS (M+H)⁺ m/z 460 (t = 2,13 min).

(S)-6-(1-hidroximetil-2-fenil-etilamina)-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-3H-pirimidin-4-ona: A una solución de (S)-2-[6-cloro-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)pirimidin-4-ilamina]-3-fenilpropan-1-ol en HCL 4 de N (0,5 ml) y ácido acético (0,5 ml) se agregaron 2 gotas de agua. La mezcla de reacción se calentó a 100°C durante 8 H, se enfrió a temperatura ambiente, y se neutralizó con amonio y metal en metanol. Después de la concentración, el residuo se purificó mediante HPLC prep. Para producir el compuesto del título (26 mg, 37% para dos etapas).

¹H
NMR (400 MHz, CD₃OD) δ 9.41 (1H, Ang t, J = 1.5 Hz), 8.06 (1H, Ang dd, J = 1.6, 1.9 Hz), 7.93 (1H, s), 7.77 (1H, Ang dd, J = 1.6, 1.8 Hz), 7.73 (1H, Ang d, J = 1.9 Hz), 7.11 – 7.21 (6H, m), 4.70 – 4.74 (1H, m), 3.74 (2H, d, J = 4.7 Hz), 3.11 (1H, dd, J = 6.1, 13.5 Hz), 3.00 (1H, dd, J = 7.8, 13.5 Hz), 2.70 (3H, s). LCMS (M+H)⁺ m/z 442 (t = 2.17 min.).

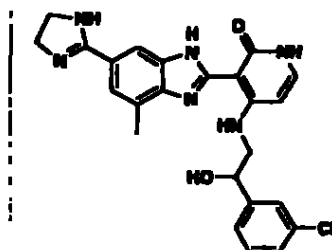
373

Ejemplo 384

(S)-3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona: el éster de imidato crudo (60 mg, 0,135 mmol) fue diluido con metanol seguido por la adición de etilenediamina (24 mg, 0,40 mmol). La mezcla de reacción fue calentada a reflujo durante 6h. Después de concentración en vacío, el residuo fue purificado por preparación HPLC para proporcionar el compuesto titulado (37 mg, 62%). ^1H RMN (300 MHz, CD_3OD) δ 7,94 (1H, s), 7,50 (1H, s), 7,50 (1H, s), 7,12-7,30 (6H, m), 6,16 (1H, d, J = 7,7 Hz), 4,04-4,10 (5H, m), 3,75-3,77 (2H, m), 3,15 (1H, dd, J = 5,2, 13,6 Hz), 2,96 (1H, dd, J = 8,1, 13,6 Hz), 2,67 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 443 (t = 1,50 min.).

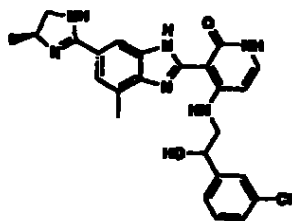
Ejemplo 385

2727
374



(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-[6-(4,5-dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2il]-1H-piridin-2-ona: ^1H RMN (300 MHz, CD_3OD) δ 7,94 (1H, s), 7,54 (1H, s), 7,23-7,45 (5H, m), 6,26 (1H, d, $J = 7,6$ Hz), 5,01 (1H, t, $J = 6,3$, Hz), 4,01 (4H, s), 3,78 (1H, dd, $J = 4,7, 13,5$ Hz), 3,67 (1H, dd, $J = 6,6, 13,5$ Hz), 2,66 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 463 ($t = 1,54$ min.).

Ejemplo 386



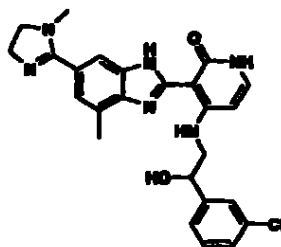
4-[2-(3-Cloro-fenil)-2*R*-hidroxi-etilamino]-3-[4-metil-6-(4*S*-metil-4,5-dihidro-1H-imidazol-2-il)-1H-benzoimidazol-2-il]-1H-piridin-2-ona y 4-[2-(3-Cloro-fenil)-2*S*-hidroxi-etilamino]-3-[4-metil-6-(4*S*-metil-4,5-dihidro-1H-

375

imidazol-2-il)-1H-benzoimidazol-2-il]-1H-piridin-2-ona:

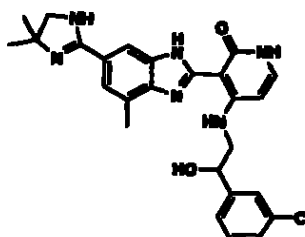
^1H RMN (300 MHz, CD_3OD) δ 7,90 (2H, s), 7,53 (2H, s), 7,22-7,47 (10H, m), 6,23 (2H, d, $J = 7,5$ Hz), 5,00 (2H, t, $J = 6,4$ Hz), 4,49-4,57 (2H, m), 4,21 (2H, t, $J = 11,0$ Hz), 3,61-3,78 (6H, m), 2,63 (6H, s), 1,48 (6H, d $J = 6,3$ Hz). LCMS $(\text{M}+\text{H})^+$ m/z 477 ($t = 1,71$ min.).

Ejemplo 387

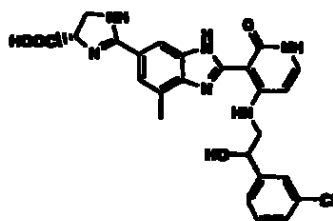


(+)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(1-metil-4,5-dihidro-1H-imidazol-2-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona: ^1H RMN (300 MHz, CD_3OD) δ 7,94 (1H, s), 7,57 (1H, s), 7,23-7,52 (5H, m), 6,22 (1H, d, $J = 7,5$ Hz), 4,99 (1H, m), 4,00-4,15 (2H, m), 3,57-3,75 (4H, m), 2,77 (3H, s), 2,61 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 477 ($t = 1,60$ min.).

376

Ejemplo 388

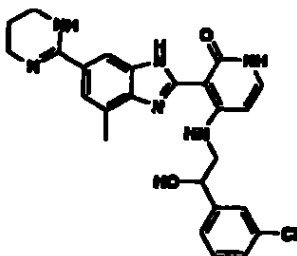
(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[6-(4,4-dimetil-4,5-dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona: ^1H RMN (300 MHz, CD_3OD) δ 7,89 (1H, s), 7,22-7,45 (5H, m), 6,19 (1H, d, $J = 7,4$ Hz), 4,99 (1H, t, $J = 6,2$ Hz), 3,84 (2H, s), 3,78 (1H, dd, $J = 4,4, 13,4$ Hz), 3,60 (1H, dd, $J = 6,7, 13,4$ Hz), 2,61 (3H, s), 1,55 (6H, s). LCMS $(\text{M}+\text{H})^+$ m/z 491 (t = 1,73 min.).

Ejemplo 389

377

2-(2-{4-[2-(3-Cloro-fenil)-2R-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-4,5-dihidro-1H-imidazol-4S-ácido carboxílico y ácido 2-(2-{4-[2-(3-Cloro-fenil)-2S-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-4,5-dihidro-1H-imidazol-4S- carboxílico: ^1H RMN (300 MHz, CD_3OD) δ 7,88 (2H, s), 7,52 (2H, s), 7,22-7,44 (10H, m), 6,17 (2H, d, $J = 7,4$ Hz), 5,05 (2H, m), 4,23-4,38 (4H, m), 3,56-3,72 (6H, m), 2,58 (6H, s),. LCMS $(\text{M}+\text{H})^+$ m/z 507 ($t = 1,64$ min.).

Ejemplo 390

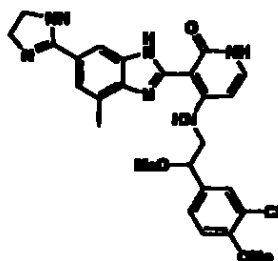


(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(1,4,5,6-tetrahidro-pirimidin-2-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona: ^1H RMN (300 MHz, CD_3OD) δ 7,90 (1H, s), 7,53 (1H, s), 7,22-7,47 (5H, m), 6,23 (1H, d, $J = 7,6$ Hz), 5,00 (1H, t, $J = 6,3$ Hz), 4,49-4,57 (1H, m), 3,60-



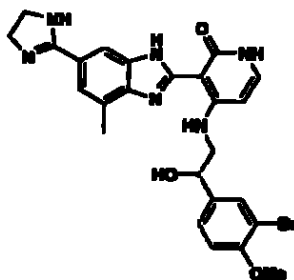
3,77 (5H, m), 3,24-3,34 (2H, m), 2,63 (3H, s). LCMS (M+H)⁺
m/z 477 (t = 1,59 min.).

Ejemplo 391



(±)-4-[2-(3-Cloro-4-metoxi-fenil)-2-metoxi-etilamino]-3-[6-(4,5-dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona: ¹H RMN (300 MHz, CD₃OD) δ 7,88 (1H, s), 7,46 (1H, s), 7,44 (1H, s), 7,31 (1H, d, J = 6,4 Hz), 7,28 (1H, d, J = 5,6 Hz), 7,01 (1H, d, J = 6,4 Hz), 6,19 (1H, d, J = 5,6 Hz), 4,49 (1H, dd, J = 3,4, 5,0 Hz), 4,09 (4H, s), 3,36 (3H, s), 3,63-3,67 (2H, m), 2,62 (3H, s). LCMS (M+H)⁺ m/z 507 (t = 1,72 min.).

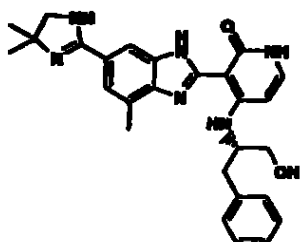
Ejemplo



379

(±)-4-[2-(3-Bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-3-[6-(4,5-dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona: El compuesto titulado fue preparado siguiendo luego de la hidrólisis del cloruro bencílico al hidroxilo. ^1H RMN (400 MHz, CD_3OD) δ 7,90 (1H, s), 7,67 (1H, s), 7,48 (1H, s), 7,38 (1H, dd, $J = 2,0$ 8,5 Hz), 7,31 (1H, d, $J = 7,6$ Hz), 6,95 (1H, d, $J = 8,5$ Hz), 6,26 (1H, d, $J = 7,6$ Hz), 4,94 (1H, m), 4,10 (4H, s), 3,80 (3H, s), 3,62-3,74 (2H, m), 2,62 (3H, s). LCMS $(\text{M}+\text{H})^+$ m/z 537 ($t = 1,49$ min.).

Ejemplo 393

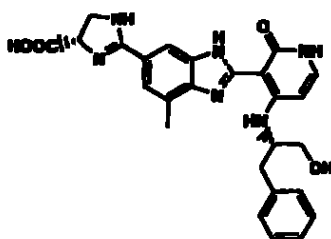


(S)-3-[6-(4,4-Dimetil-4,5-dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-4-(1-hidroxi metil-2-fenil-etilamino)-1H-piridin-2-ona: ^1H RMN (300 MHz, CD_3OD) δ 7,94 (1H, s), 7,50 (1H, s), 7,12-7,30 (6H, m), 6,15 (1H, dd, $J = 7,7$ Hz), 4,02-4,10 (1H, m), 3,85 (2H, s), 3,75-

380

3,77 (2H, m), 2,96-3,17 (2H, m), 2,67 (3H, s), 1,56 (6H, s). LCMS (M+H)⁺ m/z 471 (t = 1,62 min.).

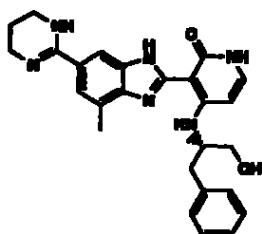
Ejemplo 394



Ácido (S)-2-{2-[4-(1S-Hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-il}-4,5-dihidro-1H-imidazol-4S-carboxilico. ¹H RMN (300 MHz, CD₃OD) δ 8,03 (1H, s), 7,60 (1H, s), 7,11-7,29 (6H, m), 6,15 (1H, d, J = 7,3 Hz), 5,07 (1H, dd, J = 6,9, 11,8 Hz), 4,25-4,41 (2H, m), 4,05-4,07 (1H, m), 3,70-3,82 (2H, m), 3,12 (1H, dd, J = 5,5, 13,6 Hz), 2,95 (1H, dd, J = 8,0, 13,6 Hz), 2,69 (3H, s). LCMS (M+H)⁺ m/z 487 (t = 1,35 min.).

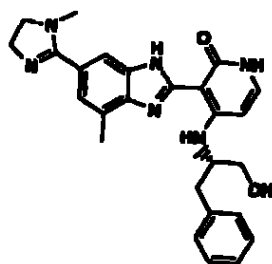
Ejemplo 395

381



(S)-4-(1-hidroximetil-2-fenil-etilamino)-3-[4-metil-6(1,4,5,6-tetrahidro-pirimidin-2-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona: ^1H RMN (300 MHz, CD_3OD) δ 7,76 (1H, s), 7,32 (1H, s), 7,09-7,29 (6H, m), 6,15 (1H, d, $J = 7,6$ Hz), 4,02-4,07 (1H, m), 3,71-3,79 (2H, m), 3,61 (4H, t, $J = 5,6$ Hz), 3,14 (1H, dd, $J = 5,3, 13,6$ Hz), 2,95 (1H, dd, $J = 8,1, 13,6$ Hz), 2,65 (3H, s), 2,09-2,16 (2H, m). LCMS $(\text{M}+\text{H})^+$ m/z 457 ($t = 1,49$ min.).

Ejemplo 396

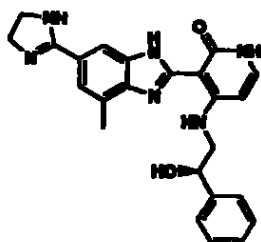


(S)-4-(1-Hidroximetil-2-fenil-etilamino)-3-[4-metil-6-(1-metil-4,5-dihidro-1H-imidazol-2-il)-1H-benzoimidazo-2-il]-1H-piridin-2-ona: ^1H RMN (300 MHz, CD_3OD) δ 7,77 (1H,

382

s), 7,10-7,30 (7H, m), 6,16 (1H, d, $J = 7,6$ Hz), 3,97-4,20 (5H, m), 3,73-3,77 (2H, m), 3,26 (3H, s), 3,15 (1H, dd, $J = 5,3, 13,6$ Hz), 2,96 (1H, dd, $J = 8,0, 13,6$ Hz), 2,68 (3H, s). LCMS (M+H)⁺ m/z 457 (t = 1,53 min.).

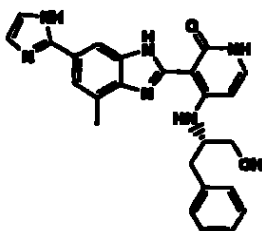
Ejemplo 397



(S)-3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-4-(2-hidroxi-2-fenil-etilamino)-1H-piridin-2-ona: ¹H RMN (400 MHz, CD₃OD) δ 7,91 (1H, s), 7,50 (1H, s), 7,48 (2H, s), 7,24-7,35 (4H, m), 6,25 (1H, d, $J = 7,6$ Hz), 5,01 (1H, dd, $J = 4,6, 7,0$ Hz), 4,10 (4H, s), 3,65-3,76 (2H, m), 2,64 (3H, s). LCMS (M+H)⁺ m/z 429 (t = 1,48 min.).

Ejemplo 398

283

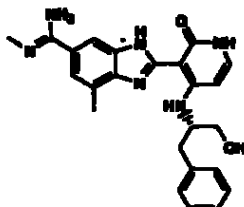


(s)-4-(1-Hidroximetil-2-fenil-etilamino)-3-[6-(1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona: a una solución de ester de imidato (150 mg, 0,31 mmol) en metanol (10 ml) se agrego aminoacetaldehido dietil acetal (97 mg, 0,93 mmol). La mezcla fue agitada a temperatura ambiente durante 14h. El disolvente fue removido en vacío y el residuo fue tratado con 60% de HClO₄ (5 ml) a temperatura ambiente durante 14h. La mezcla de reacción fue entonces neutralizada con hidróxido de amonio (conc.). La sal inorgánica fue filtrada. El filtrado fue concentrado y purificado por prep.. HPLC para proporcionar el compuesto titulado (37 mg, 27%) como un sólido blanco. ¹H RMN (300 MHz, CD₃OD) δ 7,94 (1H, narrow d, J = 1,3 Hz), 7,58 (2H, s), 7,53 (1H, narrow d, J = 0,6 Hz), 7,12-7,31 (6H, m), 6,16 (1H, d, J = 7,7 Hz), 4,04-4,08 (1H, m), 3,76-3,79 (2H, m), 3,16 (1H, dd, J = 5,4, 13,6 Hz), 3,97 (1H, dd, J = 8,1, 13,6 Hz), 2,69 (3H, s). LCMS (M+H)⁺ m/z 441 (t = 1,60 min.).

384

Procedimiento General para la Formación de Amidina,
Ejemplos 399-412 (Esquema IV, 16)

Ejemplo 399

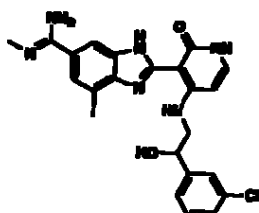


(S)-2-[4-(1-Hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7,N-dimetil-3H-benzimidazol-5-carboxamidina: El éster de imidato crudo (60 mg, 0,135 mmol) fue diluido con metanol (10 ml), luego se agrego metilamina (2,0 M en solución de metanol, 0,5 ml, exceso) a la solución. Después de agitación durante 2h, la mezcla de reacción fue concentrada y purificada por prep. HPLC para proporcionar el compuesto titulado (32 mg, 55%) como un sólido blanco.

¹H NMR (300 MHz, CD₃OD) δ 7.82 (1H, s), 7.38 (1H, s), 7.10 – 7.30 (6H, m), 6.15 (1H, J = 7.7 Hz), 4.03 – 4.07 (1H, m), 4.72 – 4.76 (2H, m), 3.06 – 3.18 (1H, m), 3.12 (3H, s), 2.96 (1H, dd, J = 8.0, 13.5 Hz), 2.67 (3H, s). LCMS (M+H)⁺ m/z 431 (t = 1.34 min.).

385

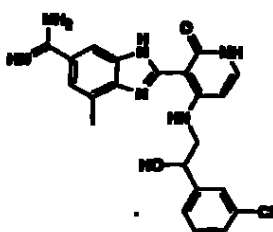
Ejemplo 400



(±)-2-{4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7,N-dimetil-3H-benzimidazol-5-carboxamidina:

¹H NMR (300 MHz, CD₃OD) δ 7.81 (1H, s), 7.54 (1H, s), 7.23 – 7.54 (5H, m), 6.26 (1H, d, J = 7.6 Hz), 5.01 (1H, t, J = 4.8 Hz), 3.77 (1H, dd, J = 4.5, 13.4 Hz), 3.67 (1H, dd, J = 6.6, 13.4 Hz), 3.12 (3H, s), 2.66 (3H, s). LCMS (M+H)⁺ m/z 451 (t = 1.32 min.).

Ejemplo 401

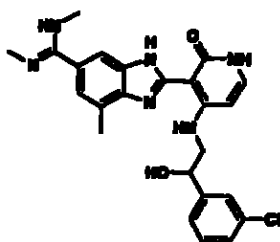


(±)-2-{4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-carboxamidina:

386

¹H NMR (300 MHz, CD₃OD)
 δ 7.90 (1H, s), 7.26–7.57 (6H, m), 6.25 (1H, d, *J* = 7.6 Hz), 5.01 (1H, t, *J* = 6.4 Hz),
 3.75 (1H, dd, *J* = 4.8, 13.4 Hz), 3.66 (1H, dd, *J* = 6.7, 13.4 Hz), 2.62 (3H, s). LCMS
 (M+H)⁺ *m/z* 437 (*t* = 1.59 min.).

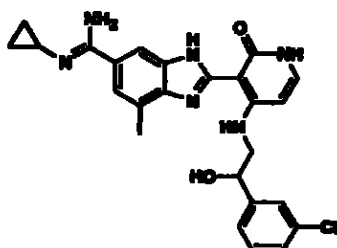
Ejemplo 402



(±)-2-(4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-
 1,2-dihidro-piridin-3-il)-7,N,N,-trimetil-3H-
 benzimidazol-5-carboxamidina:

¹H NMR (300 MHz,
 CD₃OD) δ 7.63 (1H, s), 7.54 (1H, s), 7.18–7.41 (5H, m), 6.26 (1H, d, *J* = 7.6 Hz),
 5.01 (1H, t, *J* = 6.3 Hz), 3.77 (1H, dd, *J* = 4.7, 13.5 Hz), 3.67 (1H, dd, *J* = 6.6, 13.5
 Hz), 3.34 (6H, s), 2.66 (3H, s). LCMS (M+H)⁺ *m/z* 465 (*t* = 1.57 min.).

Ejemplo 403

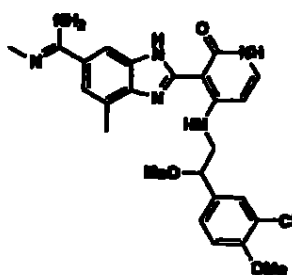


387

(±)-2-(4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-N-ciclopropil-7-metil-3H-benzimidazol-5-carboxamida:

¹H NMR (300 MHz, CD₃OD) δ 7.78 (1H, s), 7.54 (1H, s), 7.22 – 7.41 (5H, m), 6.25 (1H, d, J = 7.6 Hz), 5.01 (1H, t, J = 6.4 Hz), 3.76 (1H, dd, J = 4.7, 13.5 Hz), 3.67 (1H, dd, J = 6.6, 13.5 Hz), 2.77 – 2.83 (1H, m), 2.65 (3H, s), 1.03 – 1.10 (2H, m), 0.86 – 0.92 (2H, m). LCMS (M+H)⁺ m/z 477 (t = 1.43 min.).

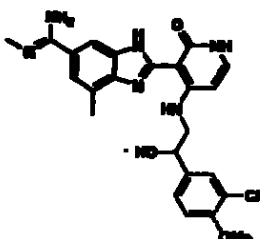
Ejemplo 404



(±)-2-(4-[2-(3-Cloro-4-metoxi-fenil)-2-metoxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7,N-dimetil-3H-benzimidazol-5-carboxamida:

¹H NMR (300 MHz, CD₃OD) δ 7.79 (1H, Ang d, J = 1.0 Hz), 7.45 (1H, Ang d, J = 1.5 Hz), 7.38 (1H, s), 7.28 – 7.31 (2H, m), 7.02 (1H, d, J = 6.4 Hz), 6.22 (1H, d, J = 5.7 Hz), 4.52 (1H, t, J = 5.9 Hz), 3.83 (3H, s), 3.60 – 3.71 (2H, m), 3.36 (3H, s), 3.13 (3H, s), 2.65 (3H, s). LCMS (M+H)⁺ m/z 495 (t = 1.64 min.).

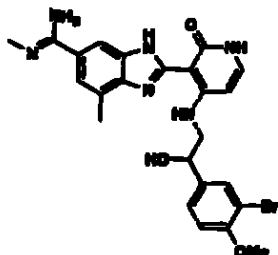
Ejemplo 405

388 ~~388~~

(±)-2-(4-[2-(3-Chloro-4-metoxi-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7,N-dimetil-3H-benzimidazol-5-carboxamidina: A una solución de 2-(4-[2-(3-cloro-4-metoxi-fenil)-2-metoxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7,N-dimetil-3H-benzimidazol-5-carboxamidina (40 mg, 0,08 mmol) en metanol (5 mL) se agrego NaOH al 2N (0,5 mL) y la mezcla de reacción fue agitada a temperatura ambiente durante 14h. Después de concentración en vacío, el residuo fue purificado por prep. HPLC para proporcionar el compuesto titulado (7,2 mg, 19%) como aceite.

¹H
NMR (300 MHz, CD₃OD) δ 7.78 (1H, d, J = 1.6 Hz), 7.52 (1H, d, J = 2.1 Hz), 7.30 – 7.36 (3H, m), 6.99 (1H, t, J = 8.5 Hz), 6.27 (1H, d, J = 7.6 Hz), 4.94 (1H, t, J = 5.9 Hz), 3.82 (3H, s), 3.68 – 3.72 (2H, m), 3.13 (3H, s), 2.63 (3H, s).
LCMS (M+H)⁺ m/z 481 (t = 1.44 min.).

Ejemplo 406



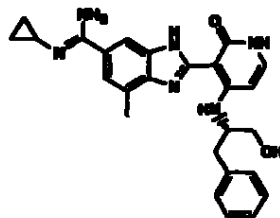
389

(±)-2-{4-[2-(3-Bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7,N-dimetil-3H-benzimidazol-5-carboxamidina:

¹H

NMR (400 MHz, CD₃OD) δ 7.77 (1H, s), 7.67 (1H, s), 7.29 – 7.39 (3H, m), 6.95 (1H, d, *J* = 8.4 Hz), 6.23 (1H, d, *J* = 4.4 Hz), 4.92 (1H, m), 3.80 (3H, s), 3.69 (2H, m), 3.13 (3H, s), 2.61 (3H, s). LCMS (M+H)⁺ *m/z* 525 (*t* = 1.44 min.).

Ejemplo 407

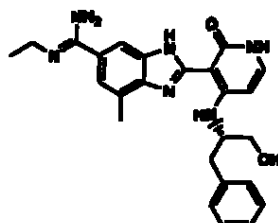


(S)-N-Ciclopropil-2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carboxamidina:

¹H NMR

(300 MHz, CD₃OD) δ 7.81 (1H, s), 7.37 (1H, s), 7.10 – 7.30 (6H, m), 6.16 (1H, d, *J* = 7.6 Hz), 4.03 – 4.08 (1H, m), 3.74 – 3.76 (2H, m), 3.15 (1H, dd, *J* = 5.3, 13.6 Hz), 2.96 (1H, dd, *J* = 8.1, 13.6 Hz), 2.78 – 2.84 (1H, m), 2.67 (3H, s), 1.03 – 1.10 (2H, m), 0.87 – 0.92 (2H, m). LCMS (M+H)⁺ *m/z* 457 (*t* = 1.51 min.).

Ejemplo 408

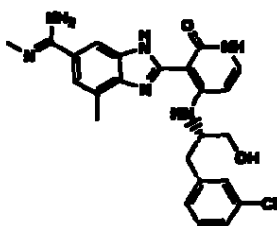


390

(S)-N-Etil-2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carboxamidina:

¹H NMR (400 MHz, CD₃OD) δ 7.82 (1H, s), 7.38 (1H, s), 7.12 – 7.30 (6H, m), 6.15 (1H, d, *J* = 7.8 Hz), 4.04 – 4.07 (1H, m), 3.75 – 3.77 (2H, m), 3.51 (2H, q, *J* = 7.3 Hz), 3.15 (1H, dd, *J* = 5.4, 13.7 Hz), 2.96 (1H, dd, *J* = 8.1, 13.7 Hz), 2.67 (3H, s), 1.40 (3H, t, *J* = 7.3 Hz). LCMS (M+H)⁺ *m/z* 445 (*t* = 1.44 min.).

Ejemplo 409

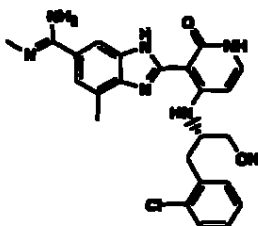


(S)-2-{4-[2-(3-Chloro-fenil)-1-hidroximetil-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7,N-dimetil-3H-benzimidazol-5-carboxamidina:

¹H NMR (400 MHz, CD₃OD) δ 7.83 (1H, s), 7.38 (1H, s), 7.31 (1H, s), 7.10 – 7.24 (4H, m), 6.16 (1H, d, *J* = 7.6 Hz), 4.06 – 4.09 (1H, m), 3.72 – 3.77 (2H, m), 3.16 (3H, s), 3.15 (1H, m), 2.96 (1H, dd, *J* = 8.2, 13.7 Hz), 2.67 (3H, s). LCMS (M+H)⁺ *m/z* 465 (*t* = 1.49 min.).

Ejemplo 410

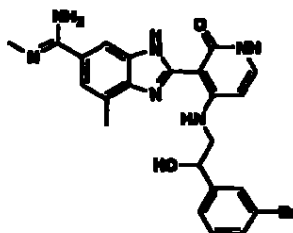
391



(S)-2-(4-[2-(2-Cloro-fenil)-1-hidroxi-metil-etil-amino]-2-oxo-1,2-dihidro-piridin-3-il)-7,N-dimetil-3H-benzimidazol-5-carboxamidina:

¹H NMR (400 MHz, CD₃OD) δ 7.84 (1H, s), 7.41 (1H, s), 7.32 – 7.35 (2H, m), 7.06 – 7.18 (3H, m), 6.10 (1H, d, *J* = 7.5 Hz); 4.20 – 4.24 (1H, m), 3.76 – 3.85 (2H, m), 3.30 – 3.34 (1H, m), 3.06 – 3.14 (1H, m), 3.13 (3H, s), 2.64 (3H, s). LCMS (M+H)⁺ *m/z* 465 (*t* = 1.48 min.).

Ejemplo 411

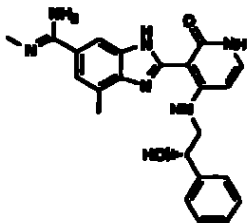


(±)-2-(4-[2-(3-Bromo-fenil)-2-hidroxi-etil-amino]-2-oxo-1,2-dihidro-piridin-3-il)-7,N-dimetil-3H-benzimidazol-5-carboxamidina:

¹H NMR (300 MHz, CD₃OD) δ 7.80 (1H, s), 7.69 (1H, s), 7.20 – 7.45 (5H, m), 6.25 (1H, d, *J* = 7.3 Hz), 5.00 (1H, t, *J* = 5.9 Hz), 3.64 – 3.80 (2H, m), 3.12 (3H, s), 2.66 (3H, s). LCMS (M+H)⁺ *m/z* 495 (*t* = 1.49 min.).

392

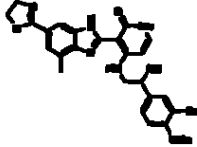
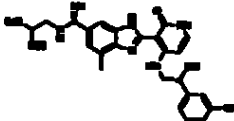
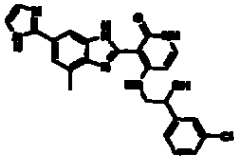
Ejemplo 412



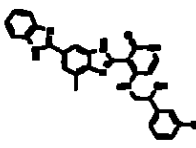
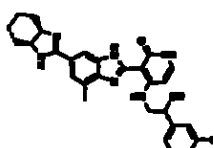
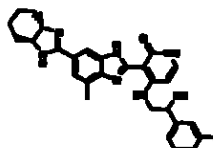
(S)-2-[4-(2-Hidroxi-2-fenilo-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7,N-dimetil-3H-benzimidazol-5-carboxamida: ¹H NMR (400 MHz, CD₃OD) δ 7,78 (1H,s), 7,24-7,49(7H,m), 6,21(1H,d, j=7,0 Hz), 4,00-5,05(1H,m), 3,61-3,74(2H,m), 3,12(3H,s), 2,63(3H,s), LCMS (M+H)⁺ m/z 417 (t=1,28 min.).

Ej. #	Nombre	Estructura	T (min.)	Masa (M+H) ⁺ m/z
413	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[6-(1-imino-1-morfolin-4-il-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1.55 (F)	507

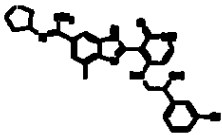
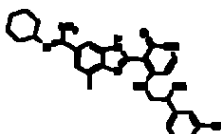
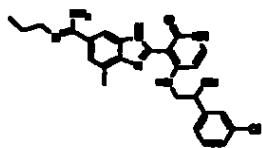
36
393

414	(±)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-[6-(4,5-dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1.49 (b)	537
415	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-(2,2-dietoxi-etil)-7-metil-3H-benzimidazol-5-carboxamidina		1.77 (f)	553
416	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[6-(1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1.71 (f)	461

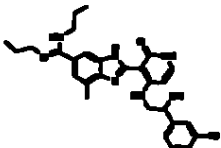
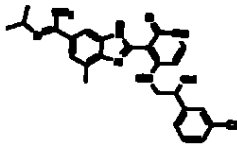
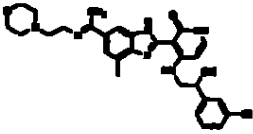
394

417	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(7'-metil-1H-, 3'H-[2,5']bibenzimidazolil-2'-il)-1H-piridin-2-ona		1.82(b)	511
418	(±)-Cis-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(7'-metil-3a,4,5,6,7,7a-hexahidro-1H,3'H-[2,5']bibenzimidazolil-2'-il)-1H-piridin-2-ona		1.75(b)	517
419	(±)-Trans-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(7'-metil-3a,4,5,6,7,7a-hexahidro-1H,3'H-[2,5']bibenzimidazolil-2'-il)-1H-piridin-2-ona		1.75(b)	517

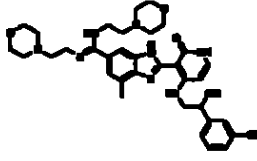
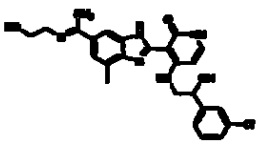
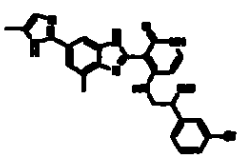
395

420	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-ciclopentil-7-metil-3H-benzimidazol-5-carboxamidina		1.55 (b)	505
421	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-ciclohexil-7-metil-3H-benzimidazol-5-carboxamidina		1.61 (b)	519
422	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-N-propil-3H-benzimidazol-5-carboxamidina		1.48 (b)	479

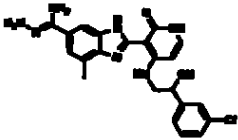
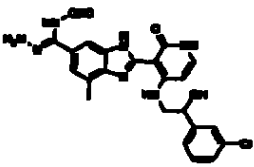
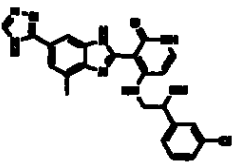
309
316

423	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-N,N'-dipropil-3H-benzimidazol-5-carboxamidina		1, 61 (b)	521
424	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-N-isopropil-7-metil-3H-benzimidazol-5-carboxamidina		1, 41 (b)	479
425	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-N-(2-morfolin-4-il-etil)-3H-benzimidazol-5-carboxamidina		1, 27 (b)	550

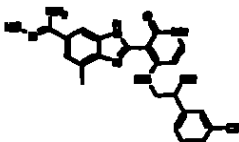
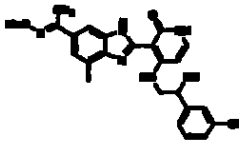
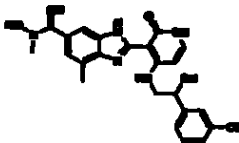


426	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-N,N'-bis-(2-morfolin-4-il-etil)-3H-benzimidazol-5-carboxamidina		1,22(b)	663
427	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-N-(2-hidroxi-etil)-7-metil-3H-benzimidazol-5-carboxamidina		138(b)	481
428	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(5-metil-1H-imidazol-2-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,62(b)	475

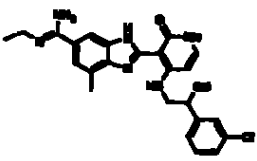
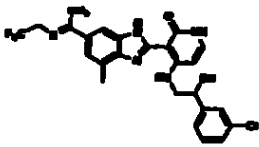
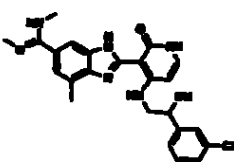
398
37/

429	Ácido (±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il} -4-metil-1H-benzimidazol-6-carboxamídico hidrazido		1,44 (f)	452
430	Ácido (±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-4-metil-1H-benzimidazol-6-carboxamídico N-formilhidrazido		1,58 (f)	480
431	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(4H-[1,2,4]triazol-3-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,82 (f)	462

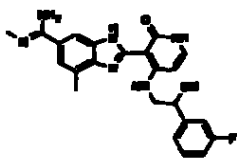
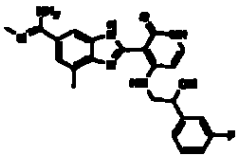
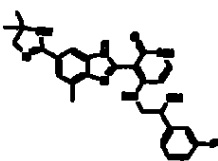
399
272

432	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-hidroxi-7-metil-3H-benzimidazol-5-carboxamidina		1, 34 (f)	453
433	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-metoxi-7-metil-3H-benzimidazol-5-carboxamidina		1, 41 (f)	467
434	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-hidroxi-7N'-dimetil-3H-benzimidazol-5-carboxamidina		1, 39 (f)	467

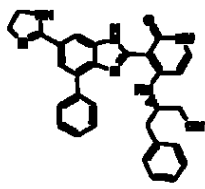
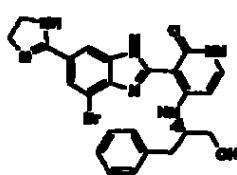
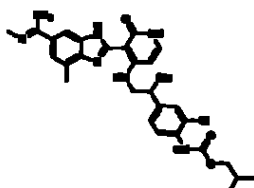
3400

435	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-etil-7-metil-3H-benzimidazol-5-carboxamidina		1,62 (f)	465
436	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-N-(2,2,2-trifluoroetil)-3H-benzimidazol-5-carboxamidina		1,75 (f)	519
437	(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7,N,N'-trimetil-3H-benzimidazol-5-carboxamidina		1,58 (f)	465

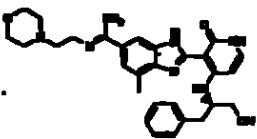
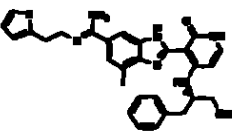
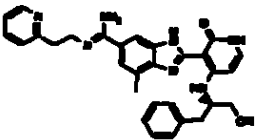
401

438	(±)-2-(4-[2-(3-fluorofenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7,N,-dimetil-3H-benzimidazol-5-carboxamidina		1,28(b)	435
439	(±)-3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-4-[2-(3-fluorofenil)-2-hidroxi-etilamino]-1H-piridin-2-ona		1,46(b)	447
440	(S)-2-[4-(1-hidroxiometil-2-feniletilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N-(2-piridin-3-il-etil)-3H-benzimidazol-5-carboxamidina		1,59(b)	475

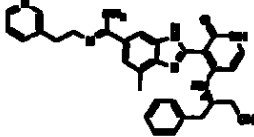
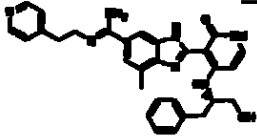
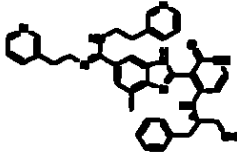
402

441	(±)-3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-fenil-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona		2, 90 (b)	505
442	(±)-3-[4,Bromo-6-(4,5-dihidro-1H-imidazol-2-il)-1H-benzimidazol-2-il]-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona		1, 57 (b)	507
443	Ácido (±)-[2-Cloro-4-(1-hidroxi-2-(3-[4-metil-6-(N-metilcarbamidomidoilo)1H-benzimidazol-2-il]-2-oxo-1,2-dihidro-piridin-4-ilamino)-etil)-fenilo]-carbámico isobutil éster		1, 64 (b)	566

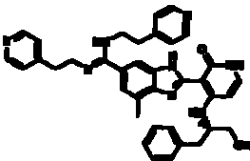
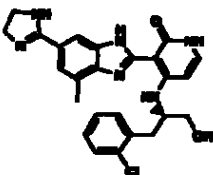
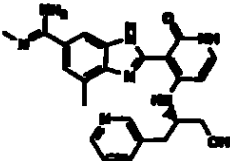
403
~~376~~

444	(S)-2-[4-(1-hidroximetil-2 fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N-(2-morfolin-4-il-etil)-3H-benzimidazol-5-carboxamidina		1.33(b)	530
445	(S)-2-[4-(1-hidroximetil-2 fenilo-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N-(2-tiofen-2-il-etil)-3H-benzimidazol-5-carboxamidina		1.62(b)	527
446	(S)-2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N-(2-piridin-2-il-etil)-3H-benzimidazol-5-carboxamidina		1.40(b)	522

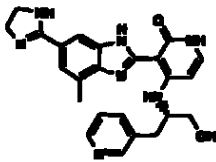
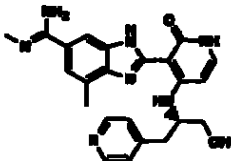
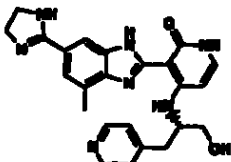
404

447	(S)-2-[4-(1-hidroxi-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N-(2-piridin-3-il-etil)-3H-benzimidazol-5-carboxamida		1.37 (b)	522
448	(S)-2-[4-(1-hidroxi-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N-(2-piridin-4-il-etil)-3H-benzimidazol-5-carboxamida		1.25 (b)	522
449	(S)-2-[4-(1-hidroxi-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N,N'-bis-(2-piridin-3-il-etil)-3H-benzimidazol-5-carboxamida		1.24 (b)	627

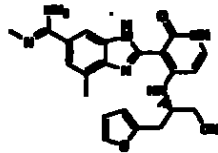
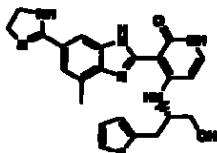
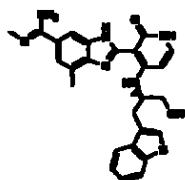
405

450	(S)-2-[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N,N'-bis-(2-piridin-4-il-etil)-3H-benzimidazol-5-carboxamidina		1.16(b)	627
451	(S)-4-[2-(2-Cloro-fenilo)-1-hidroximetil-etilamino]-3-[6-(4,5-dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1.53(b)	477
452	(S)-2-[4-(1-hidroximetil-2-piridin-3-il-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7,N-dimetil-3h-benzimidazol-5-carboxamidina		0.80(b)	432

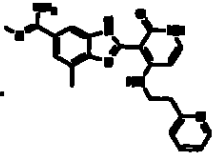
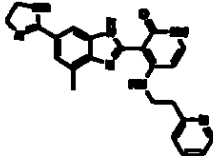
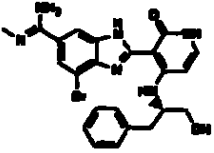
377
406

453	(s)-3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-metil-1H-imidazol-2-il)-4-(1-hidroxiometil-2-piridin-3-il-etilamino)-1H-piridin-2-ona		0.98 (b)	444
454	(S)-2-[4-(1-hidroxiometil-2-piridin-4-il-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7,N-dimetil-3h-benzimidazol-5-carboxamidina		0.73 (b)	432
455	(s)-3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il)-4-(1-hidroxiometil-2-piridin-4-il-etilamino)-1H-piridin-2-ona		0.98 (b)	444

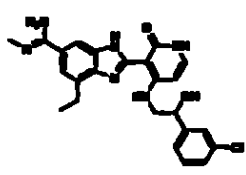
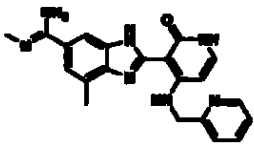
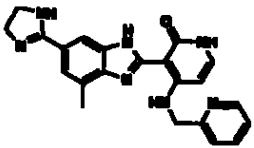
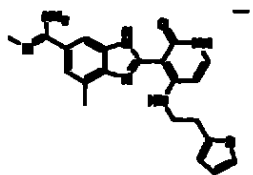
407

456	(S)-2-[4-(1-hidroxi- metil-2-tiofen-2-il-etilamino)-2-oxo- 1,2-dihidro-piridin-4-il]-7,N-dimetil-3H- benzimidazol-5-carboxamidina		1.24 (B)	437
457	(S)-3-[6-(4,5-Dihidro- 1H-imidazol-2-il)-4-metil-1H-benzimidazol- 2-il]-4-(1-hidroxi- metil-2-tiofen-2-il-etilamino)-1H- piridin-2-ona		1.46 (B)	449
458	(S)-2-[4-(1-Benzo[b]tiofen-3-il- hidroxi- metil- etilamino)-2-oxo-1,2- dihidro-piridin-3-il]- 7,N-dimetil-3H- benzimidazol-5- carboxamidina		1.47 (b)	487

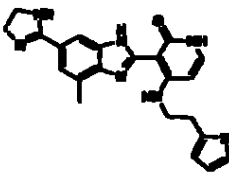
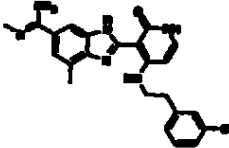
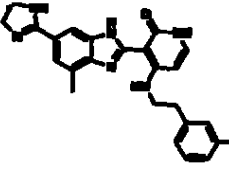
327
408

459	7,N-Dimetil-2[-2-oxo-4(2-piridin-2-il-etilamino)-1,2-dihidro-piridin-3-il]-3H-benzimidazol-5-carboxamidina		0.86(b)	402
460	3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il)-4-(2-piridin-2-il-etilamino)-1H-piridin-2-ona		0.91(B)	414
461	(S)-7-Bromol-2[4(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-diidro-piridin-3-il)-N-metil-3H-benzimidazol-5-carboxamidina		1.47(b)	495

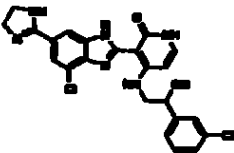
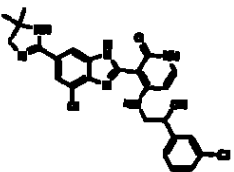
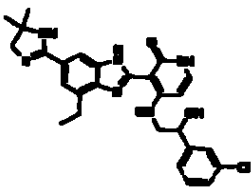
228
409

462	(±)-2-(4-[2-(3-Cloro-fenilo)2-hidroxi-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-N-metil-3H-benzimidazol-5-carboxamida		1.51 (d)	465
463	7,N-Dimetil-2[-2-oxo-4(2-piridin-2-ilmetilamino)-1,2-dihidro-piridin-3-il]-3H-benzimidazol-5-carboxamida		0.98 (b)	388
464	3-[6-(4,5-Dimetil-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]4-[(piridin-2-ilmetil)-amino]-1H-piridin-2-ona		1.07 (b)	400
465	7,N-Dimetil-2[-2-oxo-4(2-tiofen-2-il-etilamino)-1,2-dihidro-piridin-3-il]-3H-benzimidazol-5-carboxamida		1.53 (B)	407

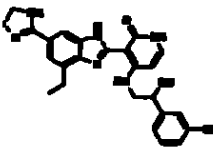
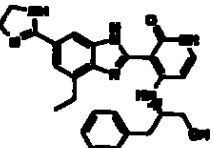
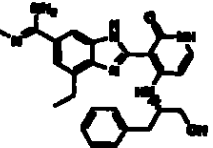
3
410

466	3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-metil-1H-benzimidazol-2-il]4-(2-tiofen-2-il-etilamina))-1H-piridin-2-ona		1.62(b)	419
467	(±)-2-{4-[2-(3-Cloro-fenilo)etilamina]-2-oxo-1,2-dihidro-piridin-3-il}-7,N-dimetil-3H-benzimidazol-5-carboxamidina		1.57(b)	435
468	(±)-4-[2-(3-Cloro-fenilo)-etilamino)-2-[6-(4,5-dihidro-1H-imidazol-3-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1.66(b)	447

284
411

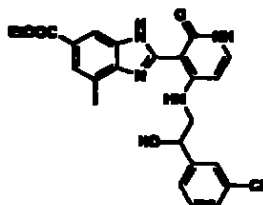
469	(±)-3-[4-Cloro-6-(4,5)-dihidro-1H-imidazol-2-il)-1H-benzimidazol-2-il]-4-[2-(3-cloro-fenilo)-2-hidroxi-etilamino]-1H-piridin-2-ona		1.40 (d)	483
470	(±)-3-[4-Cloro-6-(5,5)-dihidro-1H-imidazol-2-il)-1H-benzimidazol-2-il]-4-[2-(3-cloro-fenilo)-2-hidroxi-etilamino]-1H-piridin-2-ona		1.52 (d)	511
471	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[6-(5,5-dimetil-4,5-dihidro-1H-imidazol-2-il)-4-etil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1.57 (d)	505

328
412

472	(±)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino)-3-[6-(4,5-dihidro-1H-imidazol-2-il)-4-etil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1.49 (d)	477
473	(S)-3-[6-(4,5-Dihidro-1H-imidazol-2-il)-4-etil-1H-benzimidazol-2-il]4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona		1.47 (d)	457
474	(s)-7-etil-2[4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-n-metil-3h-benzimidazol-5-carboxamidina		1.42 (d)	445

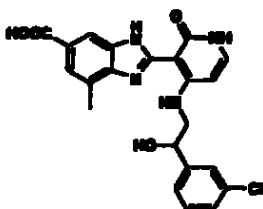
Formación de Amida

Síntesis de intermedios

276
413

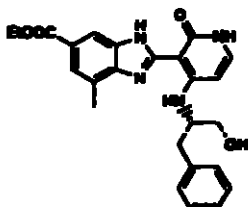
Ácido (±)-2-(4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-pyridin-3-il)-7-metil-3H-benzimidazol-5-carboxílico etil éster: una solución de ácido (±)-2-(4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il))-7 metil-3H-benzimidazol-5-carboximidico etil éster (400mg, 0,90 mmol) se diluyo con una solución HCl (20mL) al 2 N y la mezcla se le permitió agitarse a temperatura ambiente durante 14 horas. Después de concentración para secado, el producto crudo (419 mg, 100%) se utiliza para la tapa siguiente sin purificación. Pequeñas cantidades se purificaron mediante la preparación de HPLC para producir el compuesto del titulo.

^1H RMN(300 MHz, CD_3OD) δ 8,11 (1H,s), 7,74(1H,s), 7,25 (5H,m), 6,25 (1H,d, j 07,6Hz), 4,99 (1H, t j 07, 2Hz), 4,38 (2H, q, j =7,1Hz), 3,61-3,76(2H,m), 2,61(3H,s), 1,42 (3H, q, j =7,1 Hz), LCMS(M+H) $^+$ m/z 467 (t=2,23 min).

387
414

Ácido (±)-2-(4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-pyridin-3-il)-7-metil-3H-benzimidazol-5-carboxilco: el etil éster (419 mg, 0,90 mmol) obtenidos anterior mente se diluyeron con metanol (15 mL) y agua (5 ml) seguido por la adición de hidróxido de sodio (180 mg, 4,5 mmol). La mezcla se agito a temperatura ambiente durante 14 horas después de la remoción de metanol, el residuo se neutralizo con solución de HCl al 2 N la lechada resultante se filtró y lavó en agua helada. El sólido se recolecto después de secado de alto vacío. El producto crudo (395 mg, rendimiento %, puro 80%) se utilizo para la siguiente etapa sin purificación adicional

^1NMR (300 MHz, CD_3OD) δ 8,20 (1H, s), 7,92 (1H, s), 7,27-7,47 (5H, m), 6,27 (1H, d, $j=7,6\text{ Hz}$), 4,85 (1H, m), 3,63 (2H, m), 2,67 (3H, s), LCMS ($\text{M}+\text{H}$) $^+$ m/z 439 ($t=1,88\text{ min.}$).

32
415**Ejemplo 475**

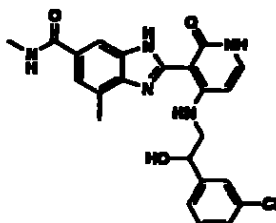
(S)-2-[4-(1-Hidroximetil-2-fenil)-etilamino]-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-Ácido ester de etilo de ácido carboxílico: El imidato éster (30 mg, 0,067 mmol) fue diluido con metanol (10 mL) y dos gotas de agua fueron agregadas. La mezcla de reacción fue agitada a temperatura ambiente durante 20h. Después de concentración en vacío, el residuo fue purificado por prep. HPLC para proporcionar el compuesto titulado (18,2 mg, 61%) como un sólido blanco.

^1H NMR (300 MHz, CD_3OD) δ 7.74 (1H, s), 7.11 – 7.30 (7H, m), 6.10 (1H, d, $J = 6.9$ Hz), 4.37 (2H, q, $J = 6.6$ Hz), 4.02 (1H, broad s), 3.69 – 3.81 (2H, m), 3.10 (1H, dd, $J = 4.8, 13.5$ Hz), 2.93 (1H, dd, $J = 7.8, 13.5$ Hz), 2.62 (3H, s), 1.41 (3H, t, $J = 6.6$ Hz). LCMS ($\text{M}+\text{H}$) $^+$ m/z 447 ($t = 1.95$ min.).

Preparación de Amidas Partiendo de ácido (±)-2-[4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-carboxílico, ejemplos 476-504, Esquema IV, 15

289
416

Ejemplo 476



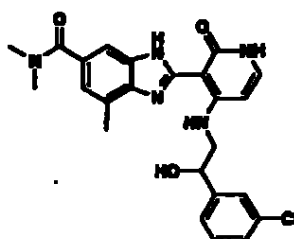
Metilamina de ácido (±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carboxílico: A una solución de ácido (50 mg, 0,11 mmol) en DMF (5 mL) se agregó azida de difenilfosforilo (38 mg, 0,14 mmol). La mezcla se le permitió agitarse durante 5 minutos. Entonces se agregó metilamina (una solución al 2,0 M en THF) (0,11 mL, 0,22 mmol). La mezcla fue agitada a temperatura ambiente durante 14h. Después de remoción del DMF con alto vacío, el residuo fue purificado por prep. HPLC para proporcionar el compuesto titulado (18 mg, 36%) como un sólido blanco.

¹H

NMR (300 MHz, CD₃OD) δ 7.89 (1H, s), 7.18 – 7.53 (6H, m), 6.23 (1H, d, *J* = 7.6 Hz), 4.98 (1H, m), 3.70 (1H, dd, *J* = 4.7, 13.5 Hz), 3.61 (1H, dd, *J* = 7.0, 13.5 Hz), 2.94 (3H, s), 2.61 (3H, s). LCMS (M+H)⁺ *m/z* 452 (*t* = 1.57 min.).

4/7

Ejemplo 477

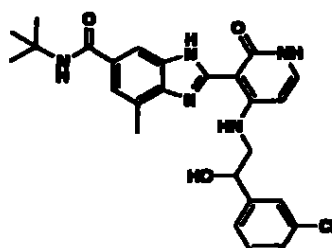


Dimetilamida de ácido (±)-2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-carboxílico:

¹H NMR

(300 MHz, CD₃OD) δ 7.52 (1H, s), 7.24 – 7.40 (5H, m), 7.15 (1H, s), 6.25 (1H, d, *J* = 7.6 Hz), 4.98 (1H, dd, *J* = 5.0, 6.9 Hz), 3.70 (1H, dd, *J* = 4.8, 13.5 Hz), 3.62 (1H, dd, *J* = 7.0, 13.5 Hz), 3.3 (3H, s), 3.08 (3H, s), 2.62 (3H, s). LCMS (M+H)⁺ *m/z* 466 (*t* = 1.84 min.).

Ejemplo 478

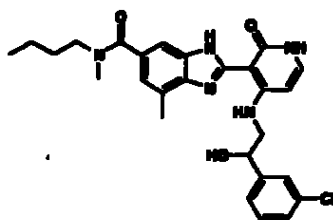


Tert-butilamida de ácido (±)-2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-carboxílico

162
35
418¹H NMR

(300 MHz, CD₃OD) δ 7.82 (1H, s), 7.53 (1H, s), 7.48 (1H, s), 7.24 – 7.40 (4H, m), 6.25 (1H, d, *J* = 7.6 Hz), 5.00 (1H, m), 3.64 – 3.70 (2H, m), 2.62 (3H, s), 1.49 (9H, s).
LCMS (M+H)⁺ *m/z* 494 (*t* = 1.79 min.).

Ejemplo 479

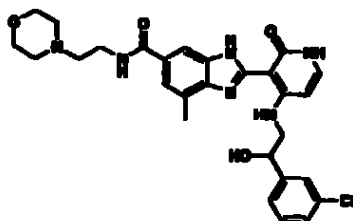


Butil-metil-amida de ácido (±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-

: ¹H NMR

(300 MHz, CD₃OD) δ 7.51 (1H, s), 7.48 (1H, s), 7.24 – 7.39 (4H, m), 7.13 (1H, s), 6.22 (1H, d, *J* = 7.6 Hz), 4.95 (1H, m), 3.55 – 3.70 (3H, m), 3.34 (1H, m), 3.05 (3H, s), 2.62 (3H, s), 0.79 – 1.69 (7H, m). LCMS (M+H)⁺ *m/z* 508 (*t* = 1.88 min.).
metil-3H-benzimidazol-5-carboxílico:

Ejemplo 480

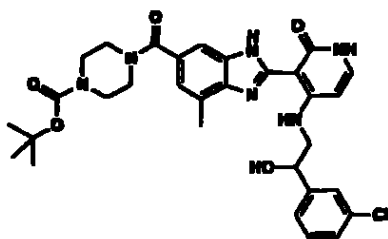


2
3
4/9

(2-morfolina-4-il-etil)-amida de ácido (±)-2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-carboxílico:

: $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 7.58 (1H, s), 7.52 (1H, s), 7.05 – 7.42 (5H, m), 6.22 (1H, d, $J = 7.6$ Hz), 4.97 (1H, dd, $J = 4.9, 6.7$ Hz), 2.60 – 4.07 (14H, m), 2.61 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 551 ($t = 1.49$ min.).

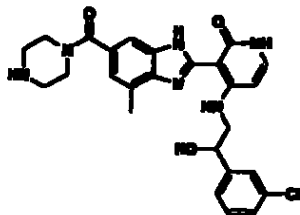
Ejemplo 481



Tert-butil éster de ácido (±)-4-[1-(2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-metanoil]-piperazina-1-carboxílico:

$^1\text{H NMR}$ (300 MHz, CD_3OD) δ 7.52 (1H, s), 7.50 (1H, s), 7.24 – 7.38 (4H, m), 7.18 (1H, m), 6.22 (1H, d, $J = 7.6$ Hz), 4.97 (1H, m), 3.49 – 3.69 (10H, m), 2.62 (3H, s), 1.47 (9H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 607 ($t = 1.90$ min.).

Ejemplo 482

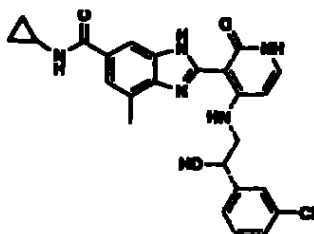


3
420

(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(1-piperazin-1-il-metanoil)-1H-benzimidazol-2-il]-1H-piridin-2-ona: A una solución de terc.butil éster de ácido (±)-4-[1-(2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-metanoil]-piperazina-1-carboxílico (40 mg, 0,06 mmol) en metanol (5mL) se agregó una solución de dioxano de HCL al 4,0 M (0,1 mL, exceso). La mezcla de reacción fue agitada a temperatura ambiente durante 14h. Después de concentración, el residuo fue purificado por prep. HPLC para dar el compuesto titulado (16 mg, 63%) como una espuma blanca.

¹H NMR (300 MHz, CD₃OD) δ 7.56 (1H, s), 7.53 (1H, s), 7.23 - 7.41 (4H, m), 7.17 (1H, m), 6.26 (1H, d, J = 7.6 Hz), 4.99 (1H, dd, J = 4.7, 6.4 Hz), 3.91 (4H, broad s), 3.74 (1H, dd, J = 4.7, 13.5 Hz), 3.65 (1H, dd, J = 6.4, 13.5 Hz), 3.31 (4H, broad s), 2.63 (3H, s). LCMS (M+H)⁺ m/z 507 (t = 1.38 min.).

Ejemplo 483



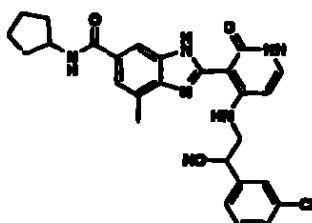
421

Ciclopropilamida de ácido (±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carboxílico:

¹H NMR

(300 MHz, CD₃OD) δ 7.80 (1H, s), 7.21 – 7.53 (6H, m), 6.22 (1H, d, *J* = 7.6 Hz), 4.99 (1H, t, *J* = 6.4 Hz), 3.59 – 3.76 (2H, m), 2.83 – 2.90 (1H, m), 2.60 (3H, s), 0.81 – 0.89 (2H, m), 0.64 – 0.73 (2H, m). LCMS (M+H)⁺ *m/z* 478 (*t* = 1.60 min.).

Ejemplo 484



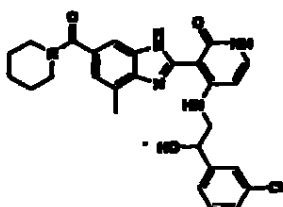
Ciclopentilamida de ácido (±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carboxílico:

¹H NMR

(300 MHz, CD₃OD) δ 7.97 (1H, s), 7.16 – 7.60 (6H, m), 6.22 (1H, d, *J* = 7.6 Hz), 4.35 (1H, m), 3.58 – 3.68 (2H, m), 2.62 (3H, s), 1.29 – 2.07 (9H, m). LCMS (M+H)⁺ *m/z* 506 (*t* = 1.86 min.).

Ejemplo 485

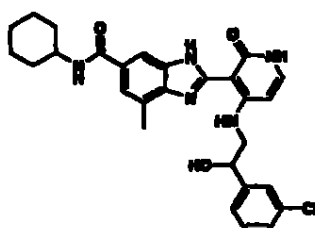
422



(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(1-piperidin-1-il-metanoil)-1H-benzoimidazol-2-il]1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 7.53 (1H, s), 7.46 (1H, s), 7.18 – 7.41 (4H, m), 7.07 (1H, s), 6.23 (1H, d, *J* = 7.6 Hz), 4.98 (1H, dd, *J* = 4.8, 6.6 Hz), 3.60 – 3.74 (5H, m), 3.18 – 3.24 (1H, m), 2.60 (3H, m), 1.43 – 1.7 (6H, m). LCMS (M+H)⁺ *m/z* 506 (*t* = 1.78 min.).

Ejemplo 486

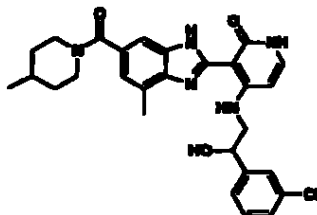


Ciclohexilamida de ácido (±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carboxílico:

¹H NMR (300 MHz, CD₃OD) δ 7.88 (1H, s), 7.54 (1H, s), 7.52 (1H, s), 7.16 – 7.40 (4H, m), 6.22 (1H, *J* = 7.6 Hz), 4.97 (1H, dd, *J* = 4.7, 6.9 Hz), 3.89 (1H, m), 3.69 (1H, dd, *J* = 4.7, 13.5 Hz), 3.61 (1H, dd, *J* = 6.9, 13.5 Hz), 2.61 (3H, s), 1.19 – 2.00 (10H, m). LCMS (M+H)⁺ *m/z* 520 (*t* = 1.93 min.).

423

Ejemplo 487

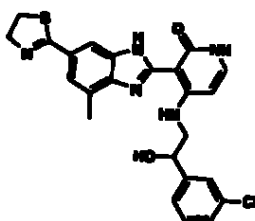


(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{4-metil-6-[1-(4-metil-piperidin-1-il)-metanoil]-1H-benzimidazol-2-il}-1H-piridin-2-ona:

¹H NMR

(300 MHz, CD₃OD) δ 7.51 (1H, s), 7.49 (1H, s), 7.21 – 7.39 (4H, m), 7.14 (1H, s), 6.24 (1H, d, *J* = 7.6 Hz), 4.96 (1H, dd, *J* = 4.7, 7.0 Hz), 3.68 (1H, dd, *J* = 4.7, 13.6 Hz), 3.60 (1H, dd, *J* = 7.0, 13.6 Hz), 2.62 (3H, s), 1.93 – 1.72 (9H, m), 1.00 (3H, d, *J* = 6.3 Hz). LCMS (M+H)⁺ *m/z* 520 (*t* = 1.97 min.).

Ejemplo 488



(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-[6-(4,5-dihidro-tiazol-2-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona: A una solución de (±)-2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-carbonitrilo (100 mg, 0,24

297
424

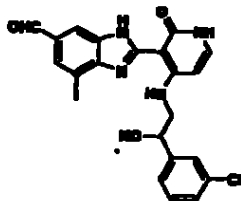
mmol) en metanol (20 mL) se agregó hidrocloreuro de 2-aminoetanotiol (41 mg, 0,36 mmol) y trietilamina (0,1 mL, exceso). La mezcla de reacción fue calentada a reflujo durante 14h y enfriada a temperatura ambiente. Después de concentración, el residuo fue purificado por prep. HPLC para proporcionar el compuesto titulado (76 mg, 66%) como un sólido amarillo.

¹H NMR (300 MHz,

CD₃OD) δ 8.10 (1H, s), 7.71 (1H, s), 7.66 (1H, s), 7.25 – 7.53 (4H, m), 6.33 (1H, d, *J* = 7.6 Hz), 5.01 (1H, dd, *J* = 4.2, 7.0 Hz), 4.58 (2H, t, *J* = 8.6 Hz), 3.91 (2H, t, *J* = 8.6 Hz), 3.73 (1H, dd, *J* = 4.2, 13.7 Hz), 3.63 (1H, dd, *J* = 7.0, 13.7 Hz), 2.64 (3H, s).

LCMS (M+H)⁺ *m/z* 480 (*t* = 1.70 min.).

Ejemplo 489



(±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbaldeído. A una suspensión de (±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carbonitrilo (76 mg, 0,18 mmol) en tolueno (anhidroso, 20 mL) se agregó disobutilaluminio (solución de tolueno al 1,4 M) (0,65 mL, 0,97 mmol) a -78°C bajo nitrógeno. La mezcla fue agitada

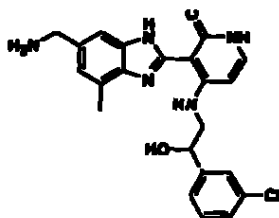
2
425

a -78°C durante 6h. Se agregó entonces acetato de etilo (1 mL) seguido por agua (0,5 mL). La mezcla fue agitada a temperatura ambiente durante 20 minutos. La mezcla fue entonces pasada a través de una almohadilla de celita y el filtrado fue concentrado. El producto crudo fue purificado por prep. HPLC para proporcionar el compuesto titulado (4 mg, 2,5%) como un sólido café.

^1H NMR (300 MHz, CD_3OD) δ 7.65

(1H, s), 7.57 (1H, s), 7.24 – 7.50 (5H, m), 6.26 (1H, d, $J = 7.6$ Hz), 5.49 (1H, s), 4.96 (1H, m), 3.53 – 3.79 (2H, m), 2.62 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 423 ($t = 1.79$ min.).

Ejemplo 490



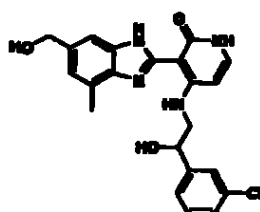
(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-[6-(1-hidroxi-1-metil-etil)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona: A una solución de etil éster de ácido (±)-2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzimidazol-5-carboxílico (40 mg, 0,08 mmol) en THF (5 mL) se agregó metil litio (solución de THF al 1,4 M, 0,57 mL, 0,08 mmol) a -78°C bajo nitrógeno. La mezcla de reacción fue gradualmente calentada a temperatura ambiente durante la

5
3
426

noche. Después de calmarla con agua, la mezcla fue particionada entre acetato de etilo y agua. Las capas orgánicas fueron lavadas con salmuera y, secadas sobre Na_2SO_4 , y concentradas en vacío. El residuo fue purificado por prep. HPLC para proporcionar el compuesto titulado (13 mg, 36%) como un aceite sin color.

^1H NMR (300 MHz, CD_3OD) δ 7.66 (1H, s), 7.47 (1H, s), 7.26 – 7.41 (5H, m), 6.26 (1H, d, $J = 7.6$ Hz), 4.92 (1H, m), 3.54 – 3.61 (2H, m), 2.62 (3H, s), 1.60 (6H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 453 ($t = 1.46$ min.).

Ejemplo 491



(±)-3-(6-aminometil-4-metil-1H-benzimidazol-2-il)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-1H-piridin-2-ona: A una solución de amida de ácido (±)-2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-carboxílico (20 mg, 0,046 mmol) en THF (1 mL) se agregó complejo de borano-tetrahidrofurano (solución al 1 M) (0,45 mL, 0,45 mmol). La mezcla de reacción fue agitada a temperatura ambiente

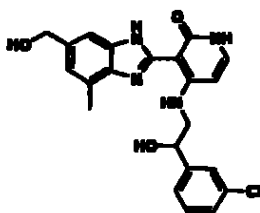
427

durante 10h y calmada con ácido acético (2 gotas). Después de la remoción de la mayor parte del solvente, el residuo fue extraído con EtOAc, lavado con salmuera, secado sobre Na₂SO₄. Después de concentración, el producto crudo fue purificado por prep. HPLC para proporcionar el compuesto titulado (11,5 mg, 60%).

¹H NMR (400

MHz, CD₃OD) δ 7.53 (1H, s), 7.50 (1H, s), 7.39 (1H, d, *J* = 7.5 Hz), 7.24 – 7.32 (3H, m), 7.13 (1H, s), 6.26 (1H, d, *J* = 7.5 Hz), 4.99 (1H, dd, *J* = 4.8, 6.8 Hz), 4.19 (2H, s), 3.72 (1H, dd, *J* = 4.8, 13.6 Hz), 3.64 (1H, dd, *J* = 6.8, 13.6 Hz), 2.62 (3H, s). LCMS (M+H)⁺ *m/z* 424 (*t* = 2.10 min.).

Ejemplo 492



(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(6-hidroxi-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona: A una solución de etil éster de ácido (±)-2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidropiridin-3-il}-3H-benzimidazol-5-carboxílico (25 mg, 0,054 mmol) en metanol (2 mL) y ácido acético (1 mL) se agregó NaBH₄ (10 mg, 0,27 mmol) a -20°C. La mezcla de reacción fue agitada a -20°C durante 30 min. y calmada con isopropanol (5 gotas). Después de la remoción de la

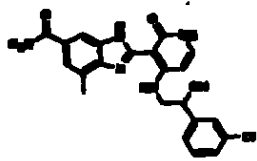
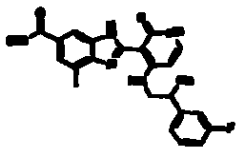
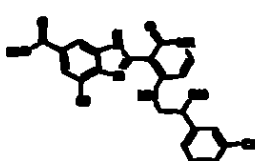
~~107~~
428

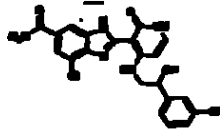
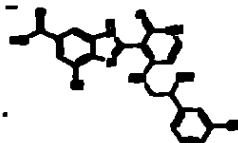
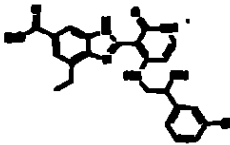
mayoría del disolvente, el residuo fue extraído con EtOAc lavado con agua y salmuera, secado sobre Na_2SO_4 . Después de concentración, el producto crudo fue purificado por prep. HPLC para proporcionar el compuesto titulado (18 mg, 62%).

^1H NMR (300 MHz, CD_3OD) δ 7.50 (1H, s), 7.48 (1H, s), 7.25 – 7.38 (4H, m), 7.22 (1H, s), 6.25 (1H, d, $J = 7.6$ Hz), 4.89 – 4.94 (1H, m), 4.76 (2H, s), 3.51 – 3.62 (2H, m), 2.62 (3H, s).

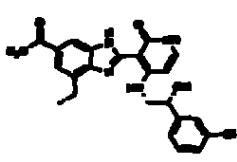
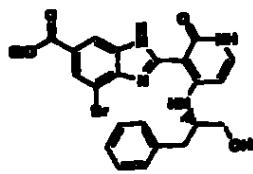
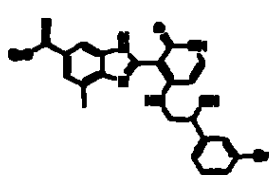
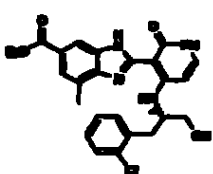
LCMS $(\text{M}+\text{H})^+$ m/z 425 ($t = 1.64$ min.).

429

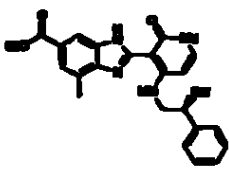
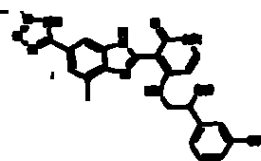
Ej. #	Nombre	BMS#	T(min)	Masa (M+H) + (m/z)
493	Ácido amida (±)-2-(4-[3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-mentil-3H-benzimidazol-5-carboxililo.		1,68 (f)	437
494	Ácido etil éster (±)-2-(4-[2-(3-Fluoro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-mentil-3H-benzimidazol-5-carboxililo.		1,90 (b)	451
495	Ácido etil éster (±)-7-Cloro -2-(4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-3H-benzimidazol-5-		2,06 (d)	467

	carboxílico.			
496	Ácido amida (±)-7-Cloro -2-{4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-3H-benzimidazol-5-carboxílico.		1,54 (d)	458
497	Ácido-(±)-7-Cloro-2-{4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-3H-benzimidazol-5-carboxílico.		1,69 (d)	459
498	Ácido etil éster-(±)-2-{4-[3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-etil-3H-benzimidazol-5-carboxílico.		1,98 (d)	481
499	Ácido amida (±)-2-{4-		1,51 (d)	452

431

	[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-etil-3H-benzimidazol-5-carboxílico.			
500	(s)-7-Bromo-2-{4-(1-hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il}-3H-benzimidazol-5-carboxílico		2,06 (b)	511
501	Ácido etil éster (±)-2-(4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-etil-3H-benzimidazol-5-carboxílico.		1,99 (b)	511
502	(S)-2-{4-[2-(3-Cloro-fenil)-2-hidroximetil-etilamino]-2-oxo-1,2-dihidro-piridin-3-		1,89 (d)	481

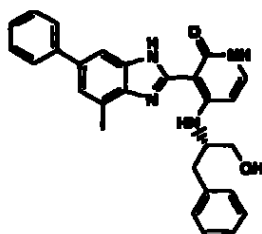
✓
\$432

	11)-7-metil-3H-benzimidazol-5-carboxílico.			
503	Ácido etil éster (S)-2-(4-(2-hidroxi-2-fenil-etilamino)-2-oxo-1,2-dihidropiridin-3-il)-7-metil-3H-benzimidazol-5-carboxílico.		1,84 (b)	433
504	(±)-4-[2-(3-Cloro fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(1H-tetrazol-5-il)-1H-benzimidazol-2-il]-piridin-2-ona.		1,84 (b)	433

Procedimiento General para los acoplamientos Suzuki,
Ejemplo 505-509 (Esquema V, 18)

Ejemplo 505

433

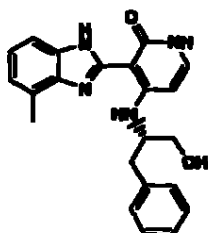


(S)-4-(1-benzil-2-hidroxi-etilamino)-3-(4-metil-6-fenil-1H-benzimidazol-2-il)-1H-piridin-2-ona: A una solución de (S)-4-(1-benzil-2-tritiloxi-etilamino)-3-[6-bromo-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona (50 mg, 0,072 mmol), ácido fenilborónico (13 mg, 0,11 mmol), y K_2CO_3 al 2 M (0,108 mL, 0,22 mmol) en THF (5 mL) se agregó $Pd(PPh_3)_4$ (8,3 mg, 0,007 mmol). La mezcla fue calentada a reflujo durante 14h. Luego de enfriamiento, la mezcla de reacción fue diluida con CH_2Cl_2 , lavada con $NaHCO_3$, saturado, secada sobre Na_2SO_4 , y concentrada en vacío. El residuo fue usado para la siguiente etapa sin purificación. LCMS $(M+H)^+$ m/z 693 (t = 2,82 min.). El producto crudo fue tratado con una solución de HCl dioxano al 4 N (5 mL) a temperatura ambiente durante 6h. Después de concentración en vacío, el residuo fue purificado por prep. HPLC para proporcionar el compuesto titulado (17 mg, 34%) como un sólido blanco.

6702
434

¹H NMR (300 MHz, CD₃OD) δ 7.13 – 7.67 (13H, m), 6.15 (1H, d, *J* = 7.4 Hz), 3.99 – 4.11 (1H, m), 3.74 – 3.77 (2H, m), 3.16 (1H, dd, *J* = 5.4, 13.6 Hz), 2.97 (1H, dd, *J* = 7.8, 13.6 Hz), 2.69 (3H, s). LCMS (M+H)⁺ *m/z* 451 (*t* = 2.04 min.).

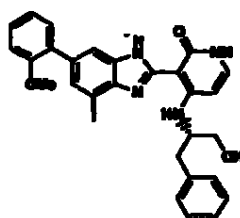
Ejemplo 506



(S)-4-(1-benzil-2-hidroxi-etilamino)-3-(4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 6.98 – 7.46 (9H, m), 6.15 (1H, d, *J* = 7.5 Hz), 3.99 – 4.04 (1H, m), 3.75 (2H, d, *J* = 5.1 Hz), 3.16 (1H, dd, *J* = 5.1, 13.6 Hz), 2.95 (1H, dd, *J* = 8.1, 13.6 Hz), 2.61 (3H, s). LCMS (M+H)⁺ *m/z* 375 (*t* = 1.72 min.).

Ejemplo 507

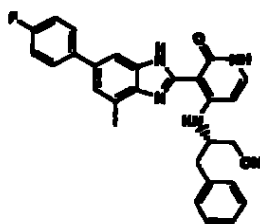


(S)-4-(1-benzil-2-hidroxi-etilamino)-3-[6-(2-metoxi-fenil)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona:

7
435

^1H NMR (300 MHz, CD_3OD) δ 6.99 – 7.59 (12H, m), 6.16 (1H, d, $J = 7.5$ Hz), 4.04 (1H, m), 3.81 (3H, s), 3.76 (2H, d, $J = 4.1$ Hz), 2.96 – 3.20 (2H, m), 2.66 (3H, s). LCMS ($\text{M} + \text{H}$) $^+$ m/z 481 ($t = 2.00$ min.).

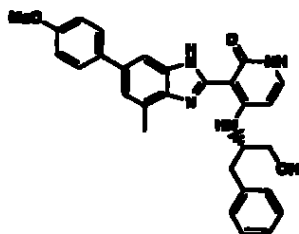
Ejemplo 508



(S)-4-(1-benzil-2-hidroxi-etilamino)-3-[6-(4-fluor-fenil)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona:

^1H NMR (300 MHz, CD_3OD) δ 7.10 – 7.66 (12H, m), 6.13 (1H, d, $J = 7.6$ Hz), 3.99 – 4.04 (1H, m), 3.76 (2H, d, $J = 5.0$ Hz), 3.16 (1H, dd, $J = 5.0, 13.6$ Hz), 2.96 (1H, dd, $J = 8.1, 13.6$ Hz), 2.65 (3H, s). LCMS ($\text{M} + \text{H}$) $^+$ m/z 469 ($t = 2.07$ min.).

Ejemplo 509



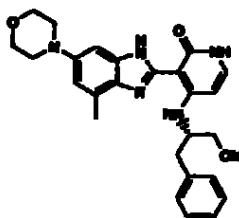
436

(S)-4-(1-benzil-2-hidroxi-etilamino)-3-[6-(4-metoxi-fenil)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 6.97 – 7.65 (12H, m), 6.14 (1H, d, *J* = 7.6 Hz), 4.00 – 4.04 (1H, m), 3.83 (3H, s), 3.76 (2H, d, *J* = 5.0 Hz), 2.95 – 3.19 (2H, m), 2.67 (3H, s). LCMS (M+H)⁺ *m/z* 481 (*t* = 2.01 min.).

Procedimiento General Para los acoplamientos Buchwald, Ejemplos 510-516 Esquema V, 19

Ejemplo 510



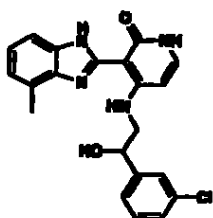
(S)-4-(1-benzil-2-hidroxi-etilamino)-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona: Una mezcla de (S)-4-(1-benzil-2-tritiloxi-etilamino)-3-[6-bromo-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona (150 mg, 0,216 mmol), morfolina (28,2 mg, 0,324 mmol), acetato de paladio (2,4 mg, 0,01 mmol), tri-tert-butilfosfina (4,4 mg, 0,02 mmol), y tert-butoxido de sodio (104 mg, 1,08 mmol) en tolueno (5 mL) fueron calentados a 100°C durante 14h bajo nitrógeno. La mezcla de reacción fue enfriada a temperatura ambiente y diluida con EtOAc.

Después de extracción, las capas orgánicas combinadas fueron lavadas con agua, salmuera, secadas sobre Na_2SO_4 . la concentración dio un residuo café, que fue tratado con una solución de dioxano y HCl al 4 N (3 mL) a temperatura ambiente durante 6h. Después de la remoción del disolvente, el residuo fue purificado por prep. HPLC para producir el compuesto titulado (18 mg, 18%).

¹H

NMR (400 MHz, CD_3OD) δ 7.59 (1H, s), 7.12 – 7.28 (7H, m), 6.12 (1H, d, $J = 7.6$ Hz), 4.01 – 4.08 (5H, m), 3.76 (1H, dd, $J = 4.8, 11.1$ Hz), 3.71 (1H, dd, $J = 5.2, 11.1$ Hz), 3.32 – 3.10 (4H, m), 3.09 (1H, dd, $J = 5.6, 13.7$ Hz), 2.92 (1H, dd, $J = 8.0, 13.7$ Hz), 2.65 (3H, s). LCMS ($\text{M}+\text{H}$)⁺ m/z 460 ($t = 1.30$ min.).

Ejemplo 511

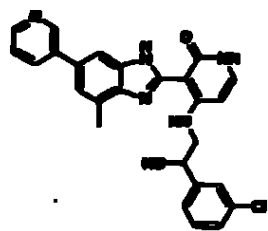


(±)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD_3OD) δ 7.17 – 7.64

(8H, m), 6.23 (1H, d, $J = 10.2$ Hz), 4.94 (1H, m), 3.61 (1H, dd, $J = 4.8, 13.8$ Hz), 3.54 (1H, dd, $J = 7.4, 13.8$ Hz), 2.61 (3H, s). LCMS ($\text{M}+\text{H}$)⁺ m/z 395 ($t = 1.65$ min.).

Ejemplo 512

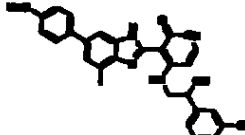
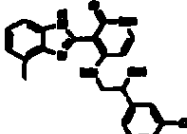
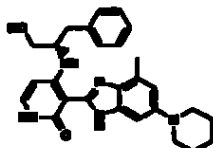


(±) -4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piridin-3-il-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 9.14 (1H, s), 8.88 (1H, d, J = 8.2 Hz), 8.72 (1H, d, J = 5.4 Hz), 8.08 (1H, dd, J = 5.8, 8.2 Hz), 7.82 (1H, s), 7.56 (1H, s), 7.24 – 7.45 (5H, m), 6.26 (1H, d, J = 7.6 Hz), 5.02 (1H, dd, J = 5.0, 6.5 Hz), 3.77 (1H, dd, J = 5.0, 13.5 Hz), 3.68 (1H, dd, J = 6.5, 13.5 Hz), 2.68 (3H, s). LCMS (M+H)⁺ m/z 472 (t = 1.66 min.).

Ej. #	Nombre	BMS #	T (min)	Masa (M+H) + (m/z)
513	(±) -3-(6-Bromo-4-metil-1H-benzimidazol-2-il) 4-[2-(3-cloro-fenil)-2-hidroxi-etilamino] 1H-piridin-2-ona		2,08 (f)	473

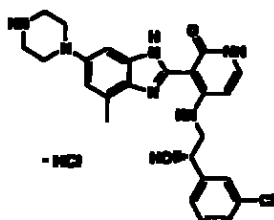
439

514	(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[6-(4-metoxi-fenil)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona		1,96(f)	501
515	(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona		1,65(f)	395
516	(S)-4-(1-Benzil-2-hidroxi-etilamino)-3-(4-metil-6-piperidin-1-il)-1H-benzimidazol-2-il)1H-piridin-2-ona		1,39(f)	458

Los siguientes ejemplo 517-519 fueron preparados de acuerdo con los esquemas VII y III

440

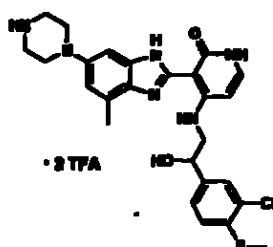
Ejemplo 517



(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona:

$^1\text{H NMR}$ (500 MHz, CD_3OD) δ 7.54 (brs, 1H), 7.40 – 7.20 (m, 4H), 7.03 (brs, 1H), 6.84 (brs, 1H), 6.25 (d, 1H, $J = 7.60$ Hz), 5.01 – 4.91 (m, 1H), 3.73 (dd, 1H), 3.65 (dd, 1H), 3.45 – 3.25 (m, 8H), 2.56 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 479,481.

Ejemplo 518

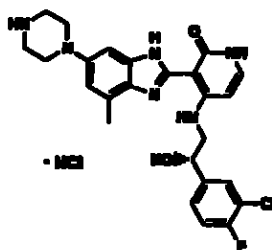


(±)-4-[2-(3-cloro-4-metilsulfanil-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona:

441

¹H NMR (500 MHz, CD₃OD) δ 7.47 (brs, 1H), 7.38 – 7.29 (m, 2H), 7.19 (d, 1H, J = 8.3 Hz), 7.03 (brs, 1H), 6.98 (brs, 1H), 6.26 (d, 1H, J = 7.7 Hz), 4.90 – 4.81 (m, 1H), 3.65 – 3.35 (m, 10H), 2.56 (s, 3H), 2.42 (s, 3H); LCMS (M+H)⁺ m/z 525, 527.

Ejemplo 519



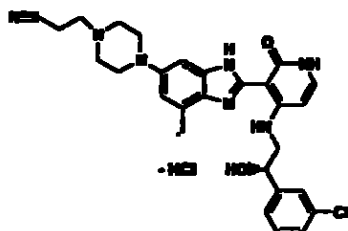
(S)-4-[2-(3-cloro-4-fluor-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (500 MHz, CD₃OD) δ 7.61 (dd, 1H, J = 2.1, 7.2 Hz), 7.40 (ddd, 1H), 7.28 (d, 1H, J = 7.5 Hz), 7.17 (dd, 1H, J = 8.9, 8.8 Hz), 7.02 (brs, 1H), 6.87 (brs, 1H), 6.25 (d, 1H, J = 7.6 Hz), 4.99 – 4.90 (m, 1H), 3.73 – 3.60 (m, 2H), 3.45 – 3.30 (m, 8H), 2.54 (s, 3H); LCMS (M+H)⁺ m/z 497, 499.

Los siguientes ejemplos (520-522) fueron preparados de acuerdo con el esquema VII y III y ilustran la alquilación de un derivado de piperazina

Ejemplo 520 (Procedimiento general para los ejemplos 520-522)

442



(S)-3-[4-(2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidropiridin-3-il}-7-metil-3H-benzoimidazol-5-il)-piperazin-1-il]-propionitrilo: A una solución agitada de 4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona (17 mg, 0,021 mmol) en metanol anhidroso (1 mL) se agregó base Hunigs (36 µL). La solución resultante fue enfriada a 0°C y se agregó acrilonitrilo (5 µL) en porciones hasta que la reacción fue completada según se juzgo por LCMS. La reacción fue calentada a temperatura ambiente y el disolvente fue evaporado en vacío. El residuo resultante fue purificado en fase inversa preparativa de HPLC usando un gradiente de metanol/agua/0,1% de ácido trifluoroacético. Las fracciones fueron evaporadas para dar el compuesto titulado como una sal de ácido trifluoroacético (12,1 mg):

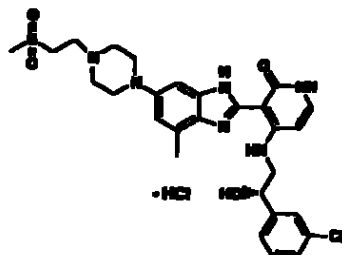
¹H NMR (500 MHz, CD₃OD) δ 7.49 (brs, 1H), 7.39 – 7.23 (m, 4H), 7.15 (brs, 1H), 7.06 (brs, 1H), 6.25 (d, 1H, J = 7.7 Hz), 4.97 – 4.88 (m, 1H), 3.70 – 3.40 (m, 12 H), 3.06 (t, 2H, J = 7.0 Hz), 2.59 (s, 3H); LCMS (M+H)⁺ m/z 532,534.

~~46~~
443

La sal de ácido trifluoroacético del compuesto puro titulado fue disuelta en metanol y aplicada a un cartucho Varian Mega Bond-Elute SCX. La elusión con metanol seguida por NH₃ al 2,0 M/MeOH dio una base libre. Este material fue suspendido en MeOH y HCL acuoso al 1,00 N (2 equivalente) fue agregado. La solución resultante fue filtrada por un filtro de 45 µm y evaporada para dar la sal de HCL bis del compuesto titulado:

¹H NMR (300 MHz, CD₃OD) δ 7.50 – 7.25 (m, 5H), 7.16 (brs, 1H), 7.13 (brs, 1H), 6.27 (d, 1H, J = 7.7 Hz), 4.95 – 4.87 (m, 1H), 3.70 – 3.40 (m, 12H), 3.13 (t, 2H, J = 7.0 Hz), 2.62 (s, 3H); LCMS (M+H)⁺ m/z 532,534.

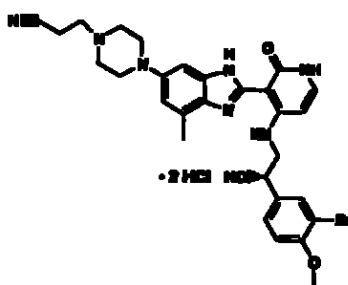
Ejemplo 521



(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(6-[4-(2-metanesulfonil-etil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il)-1H-piridin-2-ona:

¹H

NMR (500 MHz, CD₃OD) δ 7.53 (brs, 1H), 7.41 – 7.20 (m, 4H), 7.13 (brs, 1H), 6.92 (brs, 1H), 6.24 (d, 1H, J = 7.6 Hz), 5.00 – 4.92 (m, 1H), 3.80 – 3.25 (m, 14H), 3.13 (s, 3H), 2.57 (s, 3H); LCMS (M+H)⁺ m/z 585, 587.

Ejemplo 522

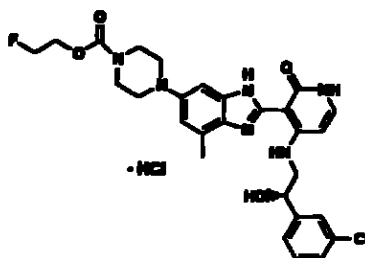
(S)-3-[4-(2-(4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il)-piperazin-1-il]-propionitrilo:

¹H NMR (500 MHz, CD₃OD) δ 7.59 (brs, 1H), 7.41 (d, 1H, J = 7.5 Hz), 7.34 (dd, 1H, J = 2.0, 8.5 Hz), 7.17 (brs, 1H), 7.12 (brs, 1H), 7.00 (d, 1H, J = 8.5 Hz), 6.25 (d, 1H, J = 7.5 Hz), 4.85 – 4.76 (m, 1H), 3.85 (s, 3H), 3.80 – 3.30 (m, 12H), 3.16 (t, 2H, J = 7.0 Hz), 2.55 (s, 3H); LCMS (M+H)⁺ m/z 606, 608.

Los siguientes ejemplos (523-528) fueron preparados de acuerdo con el esquema VII y III y ilustran la carbamoilación de un derivado de piperazina

318
445

Ejemplo 523 (procedimiento general para los ejemplos 523 a 528) fórmula)



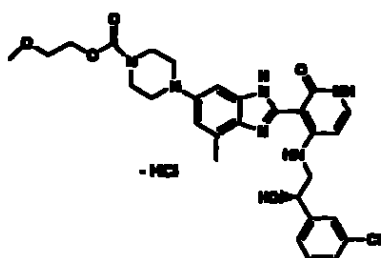
2-fluor-etil éster de ácido (S)-4-(2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il)-piperazina-1-carboxílico: A una solución agitada de 4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona (aproximadamente 2 sales de TFA, 80 mg, aproximadamente 0,1 mmol) en metanol (2 mL) a 0°C se agrego, N,N-disopropiletilamina (170 µL) y 2-fluoroetil cloroformato (37 mg). El baño de enfriamiento fue removido y la solución fue agitada a temperatura ambiente durante 30 minutos, después de los cual el análisis LC/MS mostró que la reacción estaba completa. La mezcla de reacción fue purificada sobre fase inversa preparativa de HPLC usando un gradiente de metanol/agua/ácido trifluoroacético al 0,1%. Las fracciones fueron evaporadas para dar el compuesto titulado como un sal de ácido trifluoroacético, que fue disuelta en metanol y se aplico a un cartucho de Varian

446

Mega Bond-Elute SCX. La dilución con metanol seguida por NH₃ al 2,0 M/MeOH dio la base libre (46,2 mg). Este material fue suspendido en MeOH y HCL acuoso al 1,00 N (un equivalente) fue agregado. La solución resultante fue filtrada a través de un filtro de 45 µm y evaporada para dar la sal de mono HCl del compuesto titulado (46 mg):

¹H NMR (500 MHz, CD₃OD) δ 7.50 (brs, 1H), 7.45 – 7.20 (m, 6H), 6.26 (d, 1H, J = 7.7 Hz), 4.98 – 4.91 (m, 1H), 4.64 (dm, 2H J = 47.9 Hz), 4.39 (dm, 2H, J = 29 Hz), 3.95 – 3.50 (m, 10H), 2.63 (s, 3H); . LCMS (M+H)⁺ m/z 569,571.

Ejemplo 524

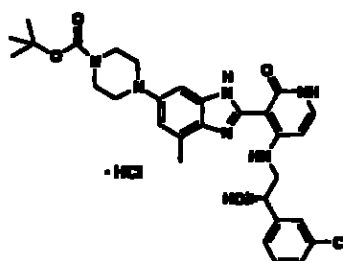


2-metoxi-etil éster de ácido (S)-4-(2-{4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-1,2-dihidro-piridin-3-il}-7-metil-3H-benzoimidazol-5-il)-piperazina-1-carboxílico:

622
447

^1H NMR (500 MHz, CD_3OD) δ 7.53 – 7.22 (m, 7H), 6.26 (d, 1H, $J = 7.6$ Hz), 4.96 (dd, 1H, $J = 7.0, 4.6$ Hz), 4.31 – 4.27 (m, 2H), 4.05 – 3.55 (m, 12H), 3.39 (s, 3H), 2.64 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 581, 583.

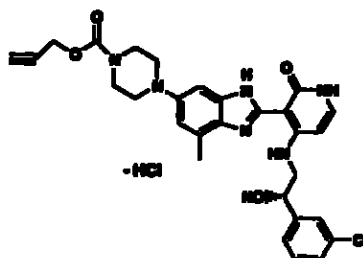
Ejemplo 525



Tert-butil éster de ácido (S)-4-(2-(4-(2-(3-cloro-fenil)-2-hidroxi-etilamino)-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il)-piperazina-1-carboxílico:

^1H NMR (500 MHz, CD_3OD) δ 7.51 (brs, 1H), 7.40 – 7.22 (m, 6H), 6.26 (d, 1H, $J = 7.7$ Hz), 4.96 – 4.90 (m, 1H), 3.90 – 3.30 (m, 10H), 2.64 (s, 3H), 1.51 (s, 9H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 579, 581.

Ejemplo 526

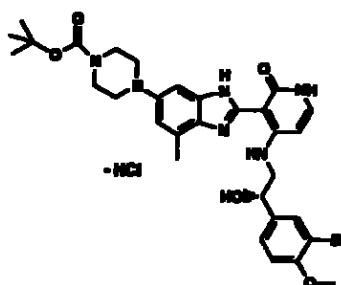


42
448

Prop-2-inil éster de ácido (S)-4-(2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il)-piperazina-1-carboxílico:

^1H NMR (500 MHz, CD_3OD) δ 7.50 (brs, 1H), 7.43 – 7.20 (m, 5H), 7.19 (brs, 1H), 6.25 (d, 1H, $J = 7.6$ Hz), 4.98 – 4.90 (m, 1H), 4.78 (d, 2H, $J = 2.5$ Hz), 3.95 – 3.30 (m, 10H), 2.97 (t, 1H, $J = 2.5$ Hz), 2.62 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 561, 563.

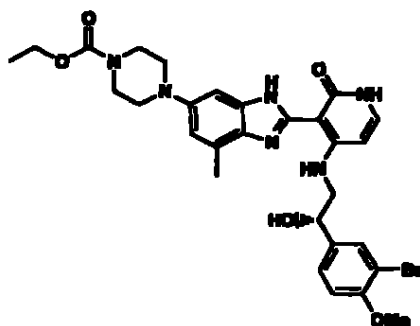
Ejemplo 527



Tert-butil éster de ácido (S)-4-(2-(4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benzoimidazol-5-il)-piperazina-1-carboxílico:

^1H NMR (300 MHz, CD_3OD) δ 7.65 (brs, 1H), 7.48 – 7.28 (m, 3H), 7.25 (brs, 1H), 6.97 (d, 1H, $J = 8.5$ Hz), 6.25 (d, 1H, $J = 7.7$ Hz), 4.94 – 4.86 (m, 1H), 3.90 – 3.45 (m, 10H), 3.82 (s, 3H), 2.61 (s, 3H), 1.52 (s, 9H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 653, 655.

Ejemplo 528



Etil éster de ácido (S)-4-(2-(4-[2-(3-bromo-4-metoxifenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil.3H-benzimidazol-5-il)-piperazina-1-carboxílico:

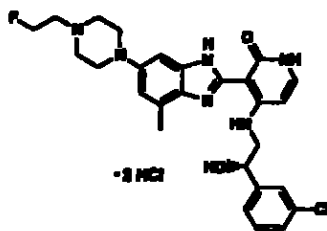
^1H NMR (400 MHz, CD_3OD) δ 7.80 (1H, s), 7.63 (1H, d, $J = 1.8$ Hz), 7.52 (1H, s), 7.42 (1H, d, $J = 7.5$ Hz), 7.37 (1H, dd, $J = 1.8, 8.4$ Hz), 7.00 (1H, d, $J = 8.4$ Hz), 6.31 (1H, d, $J = 7.5$ Hz), 4.89 (1H, m), 4.22 (2H, q, $J = 7.1$ Hz), 3.98 (4H, br s), 3.84 (3H, s), 3.70 – 3.72 (4H, m), 3.59 – 3.60 (2H, m), 2.67 (3H, s), 1.31 (3H, t, $J = 7.1$ Hz). LCMS ($\text{M}+\text{H}$) $^+$ m/z 625 ($t = 1.45$ min.).

Los siguientes ejemplos (529-540) fueron preparados de acuerdo con el esquema VII y III e ilustran un método alternativo de alquilación de un derivado de piperazina

libre (39,3 mg). Este material fue suspendido en MeOH y HCL acuoso al 1,00 N (2 equivalente) fue agregado. La solución resultante fue filtrada por un filtro de 45 μ m y evaporada para dar bis sal de HCL del compuesto titulado (43,5 mg):

¹H NMR (400 MHz, CD₃OD) δ 7.43 – 7.37 (m, 2H), 7.28 (dd, 1H, J = 2.0, 8.6 Hz), 7.16 (brs, 1H), 7.08 (d, 1H, J = 1.7 Hz), 7.01 (d, 1H, J = 8.5 Hz), 6.24 (d, 1H, J = 7.7 Hz), 4.84 – 4.78 (m, 1H), 4.60 (dt, 2H, J = 5.7, 47.1 Hz), 3.95 – 3.88 (m, 2H), 3.83 (s, 3H), 3.78 – 3.71 (m, 2H), 3.53 – 3.14 (m, 8H), 2.59 (s, 3H), 2.31 – 2.16 (m, 2H); LCMS (M+H)⁺ m/z 569, 571.

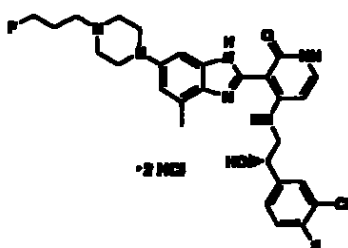
Ejemplo 530



(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-fluoro-etil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.45 – 7.20 (m, 5H), 7.16 (brs, 1H), 7.09 (brs, 1H), 6.25 (d, 1H, J = 7.6 Hz), 5.00 – 4.92 (m, 1H), 4.92 – 4.78 (m, 2H), 3.98 – 3.15 (m, 12H), 2.60 (s, 3H); LCMS (M+H)⁺ m/z 525, 527.

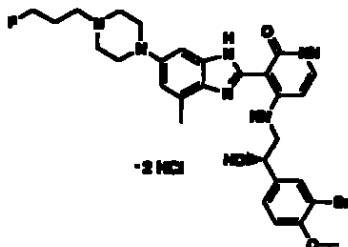
451

Ejemplo 531

(S)-4-[2-(3-cloro-4-fluoro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(3-fluoro-propil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

¹H

NMR (400 MHz, CD₃OD) δ 7.52 (dd, 1H, J = 2.1, 7.2 Hz), 7.40 (d, 1H, J = 7.6 Hz), 7.35 – 7.12 (m, 3H), 7.08 (d, 1H, J = 1.7 Hz), 6.25 (d, 1H, J = 7.7 Hz), 4.90 – 4.82 (m, 1H), 4.60 (dt, 2H, J = 5.4, 47.1 Hz), 3.96 – 3.10 (m, 12H), 2.60 (s, 3H), 2.28 – 2.13 (m, 2H); LCMS (M+H)⁺ m/z 557, 559.

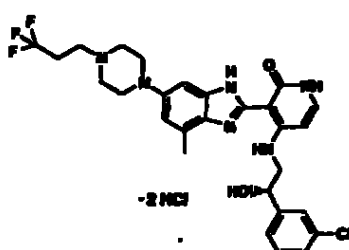
Ejemplo 532

(S)-4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-3-{6-[4-(3-fluoro-propil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

¹H

NMR (400 MHz, CD₃OD) δ 7.58 (d, 1H, J = 2.0 Hz), 7.43 (d, 1H, J = 7.6 Hz), 7.34 (dd, 1H, J = 2.0, 8.5 Hz), 7.19 (brs, 1H), 7.11 (brs, 1H), 7.00 (d, 1H, J = 8.5 Hz), 6.26 (d, 1H, J = 7.7 Hz), 5.90 – 4.82 (m, 1H), 4.61 (dt, 2H, J = 5.4, 47.1 Hz), 3.95 – 3.12 (m, 12H), 3.85 (s, 3H), 2.62 (s, 3H), 2.30 – 2.14 (m, 2H); LCMS (M+H)⁺ m/z 613, 615.

Ejemplo 533

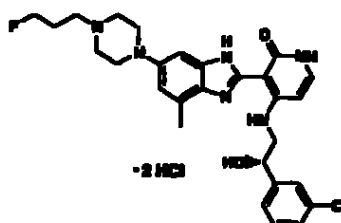


(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{4-metil-6-[4-(3,3,3-trifluoro-propil)-piperazin-1-il]-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

¹H

NMR (300 MHz, CD₃OD) δ 7.50 – 7.10 (m, 7H), 6.26 (d, 1H, J = 7.5 Hz), 4.96 – 4.88 (m, 1H), 4.00 – 3.15 (m, 12H), 3.00 – 2.82 (m, 2H), 2.61 (s, 3H); LCMS (M+H)⁺ m/z 575, 577.

Ejemplo 534

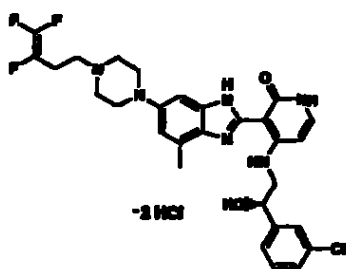


(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(3-fluoro-propil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

¹H NMR

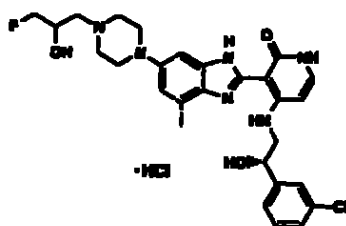
(300 MHz, CD₃OD) δ 7.46 – 7.25 (m, 5H), 7.19 (brs, 1H), 7.11 (brs, 1H), 6.27 (d, 1H, J = 7.7 Hz), 4.95 – 4.86 (m, 1H), 4.62 (dt, 2H, J = 5.4, 47.1 Hz), 3.98 – 3.15 (m, 12H), 2.62 (s, 3H), 2.35 – 2.12 (m, 2H); LCMS (M+H)⁺ m/z 539, 541.

Ejemplo 535



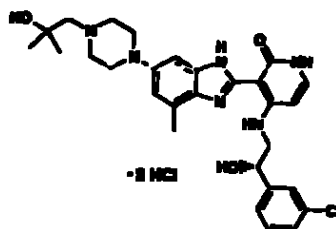
(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-[4-(3,4,4-trifluoro-but-3-enil)-piperazin-1-il]-1H-benzoimidazol-2-il)-1H-piridin-2-ona: LCMS (M+H)⁺ m/z 587, 589.

Ejemplo 536

454 ~~92~~

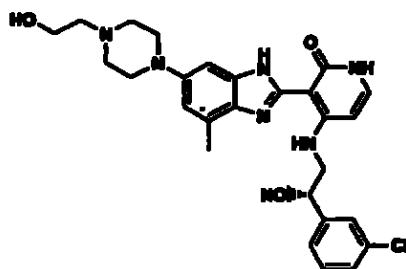
4-[2-(3-cloro-fenil)-2(S)-hidroxi-etilamino-3-{6-[4-(3-fluoro-2-hidroxi-propil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona: LCMS (M+H)⁺ m/z 555, 557.

Ejemplo 537



(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-hidroxi-2-metil-propil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

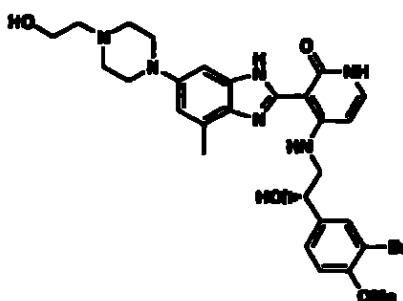
¹H
NMR (400 MHz, CD₃OD) δ 7.44 – 7.22 (m, 5H), 7.15 (brs, 1H), 7.08 (brs, 1H), 6.25 (d, 1H, J = 7.6 Hz), 4.88 – 4.80 (m, 1H), 3.86 – 3.81 (m, 4H), 3.55 – 3.32 (m, 6H), 3.28 (s, 2H), 2.60 (s, 3H), 1.38 (s, 6H); LCMS (M+H)⁺ m/z 551, 553.

455 **Ejemplo 538**

(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-hidroxi-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona:

¹HNMR (400

MHz, CD₃OD) δ 7.50 (1H, s), 7.25 – 7.35 (4H, m), 7.04 (1H, s), 6.97 (1H, s), 6.22 (1H, d, *J* = 6.8 Hz), 4.93 – 4.95 (1H, m), 3.21 – 3.96 (14H, m), 2.57 (3H, s). LCMS (M+H)⁺ *m/z* 523 (*t* = 1.11 min.).

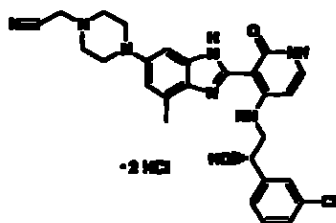
Ejemplo 539

(S)-4-[2-(3-bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-hidroxi-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona:

456 ~~456~~

^1H NMR (400 MHz, CD_3OD) δ 7.60 (1H, s, $J = 2.0$ Hz), 7.40 (1H, d, $J = 7.6$ Hz), 7.35 (1H, dd, $J = 2.0, 8.4$ Hz), 7.13 (1H, s), 7.09 (1H, s), 6.99 (1H, d, $J = 8.4$ Hz), 6.25 (1H, d, $J = 7.6$ Hz), 4.82 – 4.87 (1H, m), 3.76 – 3.97 (6H, m), 3.84 (3H, s), 3.24 – 3.52 (8H, m), 2.60 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 597 ($t = 1.09$ min.).

Ejemplo 540



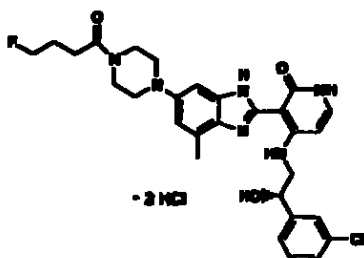
(S) - [4 - (2 - (4 - [2 - (3-cloro-fenil) - 2-hidroxi-etilamino] - 2-oxo-1,2-dihidro-piridin-3-il) - 7-metil-3H-benzoimidazol-5-il) - piperazin-1-il] - acetronitrilo:

^1H
NMR (400 MHz, CD_3OD) δ 7.50 – 7.25 (m, 7H), 6.28 (d, 1H, $J = 8.0$ Hz), 4.95 – 4.88 (m, 1H), 4.32 (s, 2H), 3.75 – 3.62 (m, 4H), 3.60 – 3.35 (m, 6H), 2.63 (s, 3H); LCMS ($\text{M}+\text{H}$) $^+$ m/z 518, 520.

Los siguientes ejemplos (541-553) fueron preparados de acuerdo con los esquemas 7 y 3 e ilustran la acilación de un derivado de piperazina

457 

Ejemplo 541 (Procedimiento general para los ejemplos 541-553)



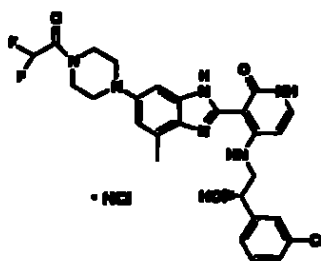
(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(4-fluoro-butiril)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona: A una solución agitada de 4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona (70 mg, 0,136 mmol) en N,N- dimetilformamida anhidrosa (750 μ L) se agregó hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (112 mg, 0,584 mmol), hidrato de 1-hidroxibenzotriazol (59 mg, 0,438 mmol), N-metilmorfolina (0,048 mL, 0,438 mmol) y ácido 4-fluorobutilico (31 mg, 0,291 mmol; ver O'Hagan, D., J. Fluorine Chem., 43, (1989), 371-377) y la mezcla fue calentada a 80°C durante 3h. La mezcla de reacción fue entonces purificada sobre fase inversa preparativa de HPLC usando un gradiente de metanol/agua/ácido trifluoroacético al 0,1%. Las fracciones fueron evaporadas para dar el compuesto titulado como una sal de ácido trifluoroacético que fue disuelta en metanol y

458

aplicada a un cartucho de Varian Mega Bond-Elute SCX. La elusión con metanol seguida por NH₃ al 2,0 M/MeOH dio la base libre (35,9 mg). Este material fue suspendido en MeOH y HCL acuosos al 1,00 N (2 equivalente) fue agregado. La solución resultante fue filtrada por un filtro de 45 µm y evaporada para dar la sal bis HCl del compuesto titulado (37,6 mg):

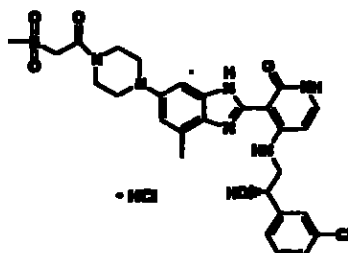
¹H NMR (400 MHz, CD₃OD) δ. 7.61 (brs, 1H), 7.47 (brs, 1H), 7.44 – 7.20 (m, 5H), 6.27 (d, 1H, J = 7.6 Hz), 4.92 (dd, 1H, J = 4.4, 7.3 Hz), 4.50 (dt, 2H, J = 5.9, 47.3 Hz), 4.05 – 3.40 (m, 10H), 2.64 (s, 3H), 2.63 (t, 2H, J = 7.6 Hz), 2.09 – 1.95 (m, 2H); LCMS (M+H)⁺ m/z 567,569.

Ejemplo 542



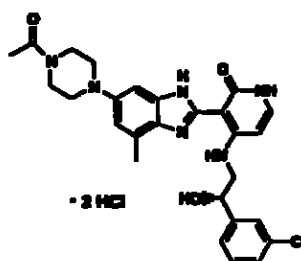
(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2,2-difluoro-acetil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona: LCMS (M+H)⁺ m/z 557,559.

Ejemplo 543

22
459

(S)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-metanesulfonil-acetil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona: LCMS (M+H)⁺ m/z 599, 601.

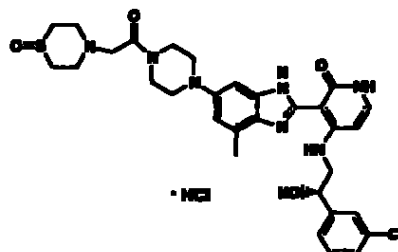
Ejemplo 544



(S)-3-[6-(4-acetil-piperazin-1-il)-4-metil-1H-benzoimidazol-2-il]-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-1H-piridin-2-ona:

¹H NMR (500 MHz, CD₃OD) δ 7.57 (brs, 1H), 7.49 (brs, 1H), 7.40 – 7.20 (m, 5H), 6.29 (d, 1H, J = 7.6 Hz), 4.98 – 4.90 (m, 1H), 4.02 – 3.91 (m, 4H), 3.70 – 3.50 (m, 6H), 2.66 (s, 3H), 2.21 (s, 3H); LCMS (M+H)⁺ m/z 521, 523.

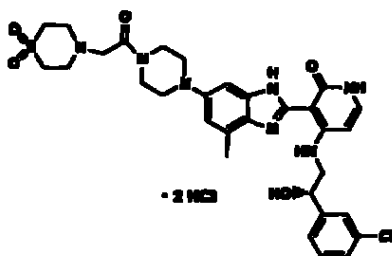
Ejemplo 545



(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-{4-[2-(1-oxo-1H-tiomorfolina-4-il)-acetil]-piperazin-1-il}-1H-benzoimidazol-2-il)-1H piridin-2-ona:

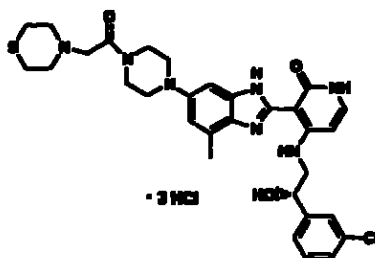
LCMS (M+H)⁺ m/z 638, 640.

Ejemplo 546

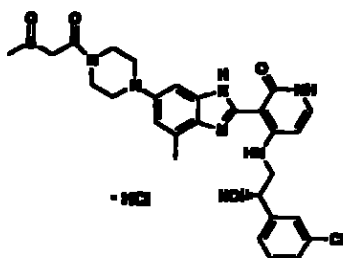


(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-{4-[2-(1,1-dioxo-1 16-tiomorfolina-4-il)-acetil]-piperazin-1-il}-4-metil-1H-benzoimidazol-2-il)-1H piridin-2-ona:

LCMS (M+H)⁺ m/z 654, 656

461 ~~25~~**Ejemplo 547**

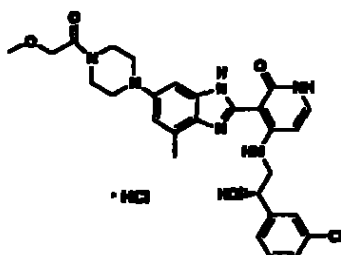
(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-[4-(2-tiomorfolin-4-il-acetilo)-piperizin-1-il]-1H-benzoimidazol-2-il)-1H-piridin-2-ona: LCMS (M+H)⁺ m/z 622, 624

Ejemplo 548

4-[2-(3-Cloro-fenilo)-2 (S)-hidroxi-etilamino]-3-{6-[4-(2-metanesulfonil-acetilo)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il)-1H-piridin-2-ona: LCMS (M+H)⁺ m/z 582, 585.

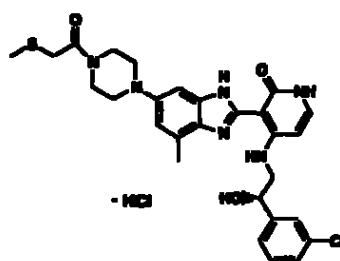
462

Ejemplo 549



(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6[4-(2-metoxi-acetil)-piperazin-1-il]-4-metil-1H-benzoimidazol-2-il)-1H-piridin-2-ona: ^1H NMR (500MHz, CD_3OD) δ 7,49 (brs, 1H), 7,40-7,18(m, 6H), 6,26(d, 1H, $J = 7,7$ Hz), 4,98-4,90(m, 1H), 4,25(s, 2H), 3,95-3,45 (m, 10H), 3,44 (s, 3H); LCMS $(\text{M}+\text{H})^+$ m/z 551,553.

Ejemplo 550

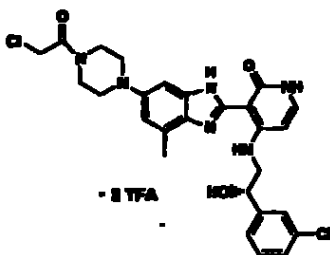


(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-[4-(2-metilsufanil-aceril)-piperazin-1-il]-1H-benzoimidazol-2-il)-1H-piridin-2-ona: ^1H NMR (500MHz,

36
463

CD₃OD) δ 7.49 (brs, 1H), 7.45-7.20 (m, 6H) 6.26 (d, 1H, $J=7.60$ Hz), 4.98-4.90 (m, 1H), 3.97-3.40 (m, 12H), 2.63 (s, 3H), 2.20 (s, 3H); LCMS (M+H)⁺ m/z 567, 569.

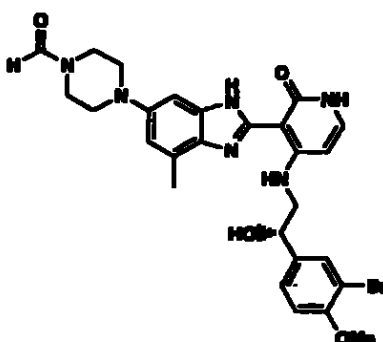
Ejemplo 551



(S)-3-{6-[4(2-Cloro-acetil)-piperazin-1-il]-metil-1H-benzoimidazol-2-il}-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-1H piridin-2-ona: ¹H NMR (500 MHz, CD₃OD) δ 7,49 (brs, 1H), 7,38-7,20 (m, 5H), 7,15 (brs, 1H), 6,25 (d, 1H, $j = 7,6$ Hz) 4,98-4,90 (m, 1H), 4,355H), (s, 2H), 3,90-3,80 (m, 4H), 3,66-3,30 (m, 6H), 2,61 (s, 2H); LCMS (M+H)⁺ m/z 555, 557.

Ejemplo 552

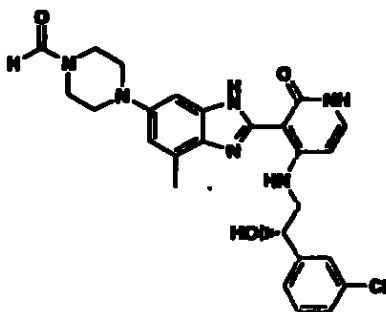
338
464



(S)-4-(2(4-[2(3-Bromo-4-Metoxi-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il)-7-metil-3H-benziminidazol-5-il)-piperazina-1-carbaldehído:

^1H NMR (400 MHz, CD_3OD) δ 8.18 (1H, s), 7.65 (1H, s), 7.61 (1H, narrow d, $J = 2.0$ Hz), 7.46 (1H, s), 7.43 (1H, d, $J = 7.6$ Hz), 7.36 (1H, dd, $J = 2.0, 8.5$ Hz), 7.00 (1H, d, $J = 8.5$ Hz), 6.32 (1H, d, $J = 7.6$ Hz), 4.86 – 4.89 (1H, m), 3.91 – 3.96 (4H, m), 3.84 (3H, s), 3.57 – 3.67 (7H, m), 2.66 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 581 ($t = 1.24$ min.).

Ejemplo 553



~~465~~
465

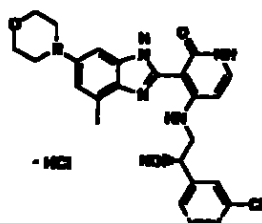
(S)-4-(2-(4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridina-3-il)-7-metil-3H-benzimidazol-5-il)-piperacina-1-carbaldehído:

¹H

NMR (400 MHz, CD₃OD) δ 8.12 (1H, s), 7.50 (1H, s), 7.24 – 7.38 (6H, m), 6.23 (1H, d, J = 7.6 Hz), 4.93 – 4.96 (1H, m), 3.54 – 3.79 (10H, m), 2.58 (3H, s). LCMS (M+H)⁺ m/z 507 (t = 1.29 min.).

Los siguientes ejemplos (554-575) fueron preparados de acuerdo con los esquemas VII y III

Ejemplo 554



(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-morfolina-4-il-1H-benzoimidazol-2-il)-1H piridin-2-ona: a una suspensión de 4-Cloro-3(4-metil-6-morfolin-4-il-1H-benzoimidazol-2-il)-1H-piridin-2-ona y el compuesto de yodo correspondiente 4-Yodo-3-(4-metil-6-morfolin-4-il-1H-benzoimidazol-2-il)-1H-piridin-2-ina (4.43g, ~ 11 mmol) en acetonitrilo (100 ml) trietilamina (7,0 ml, 50 mmol) y 2-(S)-2-(3-Cloro-fenil)-2-hidroxi-



etilamina hidrocloreuro (2,55 g, 12,2 mmoles) fueron agregados. La mezcla fue agitada a 85°C durante la noche. El LCMS mostró que algo del material de partida de piridona dejado 2-(S)-2-(3-cloro-fenil)-2-hidroxi-etilamina hidrocloreuro (0,22 g, 1,06 mmoles) fue agregado y la mezcla fue agitada a 85°C durante otras 24 horas. Después de la evaporación de los volátiles en solución acuosa de Cs₂CO₃ (200 ml, 10%) fue agregada, la suspensión sonicada por 5 minutos y agitada durante la noche. El producto fue filtrado, lavado con agua y recristalizado de metanol-cloroformo. El compuesto titulado fue aislado como cristales amarillos. (3,951 g, 75%). LCMS (M+H)⁺ m/z 480 (t = 1,31 minutos). HPLC t = 4,93 min, paquete YMC ODS-A 3.0 x 50 mm; gradiente 0 - 100% sobre 8 min; índice de flujo 2,5 ml/min. ¹H RMN de sal de HCl

(500 MHz, DMSO-d₆) δ 13.3 (1H, ^{Ampl} s), 11.22 (1H, s), 10.9 (1H, ^{Ampl} s), 7.65 (1H, ^{Ampl} s), 7.60 (1H, s), 7.45 (d, J = 7.6 Hz), 7.38-7.30 (4H, m) 6.19 (1H, d, J = 7.5 Hz), 4.92 (1H, t, J = 5.3 Hz), 4.00 (6H, ^{Ampl}), 3.67 (1H, m), 3.52 (5H, m), 2.58 (3H, s).

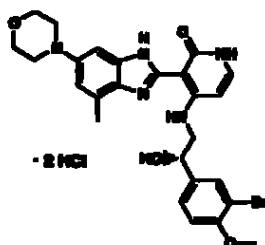
Procedimiento general para la preparación de sales mono- y bis- HCL:

Una solución o suspensión de base libre en metanol es tratada con 1,00 (o 2,00 de respuesta) equivalente a 1,00

467

N de HCL acuoso. Si cantidades significativas del compuesto permanecen insolubles en igual volumen de dicloroetano es agregado para mejorar la solubilidad. La mezcla es filtrada y concentrada en vacío. Pequeñas cantidades fueron evaporadas hasta secadas, preparaciones a gran escala para estudios en vivo fueron concentradas hasta que la mayoría de los compuestos cristalizados, fueron filtrados.

Ejemplo 555

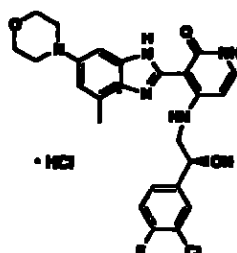


(S)-4-[2-(3-Bromo-4-Metoxi-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-morfolina-4-il-1H-benzoimidazol-2-il)-1H-piridina-2-ona:

¹H NMR (300 MHz, CD₃OD) δ 7.68 – 7.60 (m, 2H), 7.43 – 7.28 (m, 3H), 6.98 (d, 1H, J = 8.50 Hz), 6.26 (d, 1H, J = 7.7 Hz), 4.97 – 4.89 (m, 1H), 4.18 – 4.04 (m, 4H), 3.82 (s, 3H), 3.73 – 3.55 (m, 6H), 2.63 (s, 3H); LCMS (M+H)⁺ m/z 554, 556.

~~468~~

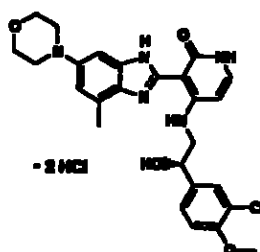
Ejemplo 556



(s)-4-[2-(3-cloro-4-fluoro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-morfolina-4-il-1H-benzoimidazol-2-il)-1H-piridina-2-ona):

¹H NMR (300 MHz, CD₃OD) δ 7.65 – 7.50 (m, 2H), 7.43 – 7.20 (m, 3H), 7.18 (dd, 1H, J = 8.9, 8.8 Hz), 6.27 (d, 1H, J = 7.6 Hz), 5.00 – 4.91 (m, 1H), 4.15 – 4.02 (m, 4H), 3.75 – 3.60 (m, 6H), 2.64 (s, 3H); LCMS (M+H)⁺ m/z 498, 500.

Ejemplo 557

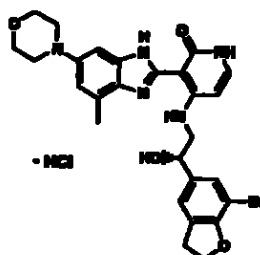


(s)-4-[2-(3-Cloro-4-metoxi-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-morfolina-4-il-1H-benzoimidazol-2-il)-1H-piridina-2-ona:

2
469

¹H NMR (400 MHz, CD₃OD) δ 7.67 (brs, 1H), 7.45 (brs, 1H), 7.40 – 7.28 (m, 3H), 7.00 (d, 1H, J = 8.4 Hz), 6.27 (d, 1H, J = 7.6 Hz), 4.95 – 4.84 (m, 1H), 4.15 – 4.05 (m, 4H), 3.82 (s, 3H), 3.75 – 3.55 (m, 6H), 2.64 (s, 3H); LCMS (M+H)⁺ m/z 510, 512.

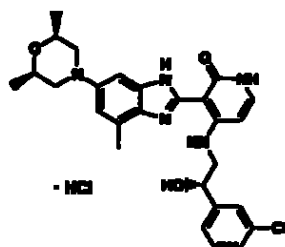
Ejemplo 558



(S)-4-[2-(7-Bromo-2,3-dihidro-benzofuran-5-il)-2-hidroxi-etilamino]-3-(4-metil-6-morfolina-4-il-1H-benzoimidazol-2-il)-1H-piridina-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.54 (brs, 1H), 7.35 – 7.30 (m, 2H), 7.27 (brs, 1H), 7.22 (brs, 1H), 6.27 (d 1H, J = 7.6 Hz), 4.95 – 4.87 (m, 1H), 4.60 – 4.50 (m, 2H), 4.10 – 4.00 (m, 4H), 3.75 – 3.60 (m, 6H), 3.25 – 3.13 (m, 2H), 2.62 (s, 3H); LCMS (M+H)⁺ m/z 566, 568.

Ejemplo 559

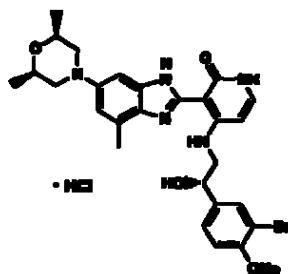


4-[2-(3-Cloro-fenil)-2(S)-hidroxi-etilamino]-3-[4-metil-6-[2(S), 6-(R)-dimetil-morfolina-4-il]-1H-benzoimidazol-2-il]-1H-piridina-2-ona.

¹H NMR

(400 MHz, CD₃OD) δ 7.23-7.57 (7H, -m), 6.22 (1H, d, J = 7.6 Hz), 4.97 (1H, m), 4.06 (2H, m), 3.62-3.68 (4H, m), 3.20-3.34 (2H, m), 2.63 (3H, s), 1.30 (6H, d, J = 6.28 Hz), LCMS (M+H)⁺ m/z 508 (t = 2.12 min.)

Ejemplo 560

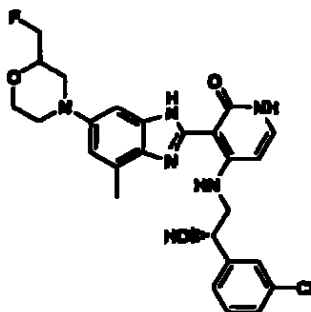


4-[2-(3-Bromo-4-metoxi-fenil)-2-(S)-hidroxi-etilamino]-3-[4-metil-6-[2(S)-6-(R)-dimetil-morfolina-4-il]-1H-benzoimidazol-2-il]-1H-piridina-2-ona:

47

^1H NMR (400 MHz, CD_3OD) δ 7.73 (1H, s), 7.63 (1H, s), 7.42 (1H, s), 7.34 (2H, m), 6.96 (1H, d, $J = 8.48$ Hz), 6.21 (1H, d, $J = 7.48$ Hz), 4.87 (1H, m), 4.23 (2H, m), 3.57-3.67 (4H, m), 3.34 (3H, s) 3.30-3.32 (2H, m), 2.60 (1H, s), 1.30 (6H, d, $J = 6.2$ Hz) LCMS ($\text{M}+\text{H}$) $^+$ m/z 582 ($t = 2.03$ min.)

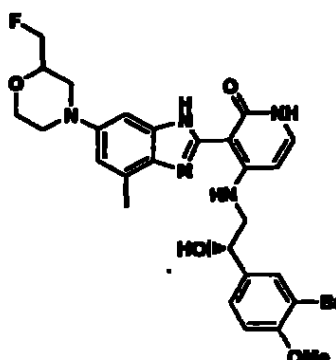
Ejemplo 561



4-[2-(3-Cloro-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(R)-2-fluorometil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridina-2-ona y 4-[2-(3-cloro-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(S)-2-fluorometil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

^1H NMR (400 MHz, CD_3OD) δ 7.47 (1H, s), 7.23 – 7.43 (6H, m), 6.22 (1H, d, $J = 7.2$ Hz), 4.87 – 4.94 (1H, m), 4.60 (1H, d, $J = 3.4$ Hz), 4.48 (1H, d, $J = 3.4$ Hz), 4.04 – 4.15 (3H, m), 3.28 – 3.62 (6H, m), 2.56 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 512 ($t = 1.35$ min.).

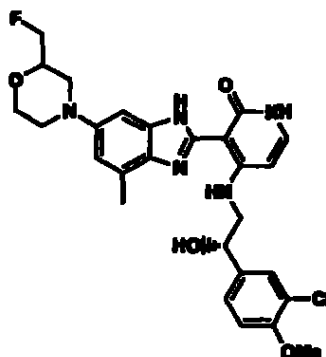
Ejemplo 562



4-[2-(3-Bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(R)-2-fluorometil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridina-2-ona y 4-[2-(3-Bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(S)-2-fluorometil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

^1H NMR (400 MHz, CD_3OD) δ 7.60 (1H, Ang d, $J = 2.0$ Hz), 7.56 (1H, s), 7.39 (1H, br s), 7.34 (1H, dd, $J = 2.0, 8.4$ Hz), 6.97 (1H, d, $J = 8.4$ Hz), 6.27 (1H, d, $J = 6.4$ Hz), 4.86 (1H, m), 4.61 (1H, m), 4.50 (1H, m), 4.77 – 4.19 (3H, m), 3.82 (3H, s), 3.38 – 3.74 (8H, m), 2.63 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 586 ($t = 1.31$ min.).

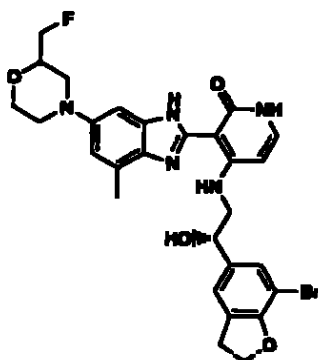
Ejemplo 563



4-[2-(3-Cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(R)-2-fluorometil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridina-2-ona y 4-[2-(3-Cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(S)-2-fluorometil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridina-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.45 (1H, s), 7.28 – 7.30 (3H, m), 7.10 (1H, s), 6.97 (1H, d, J = 8.0 Hz), 6.20 (1H, d, J = 6.4 Hz), 4.85 (1H, m), 4.58 (1H, br s), 4.46 (1H, br s), 3.93 – 4.10 (3H, m), 3.80 (3H, s), 3.59 (4H, m), 3.07 – 3.29 (2H, m), 2.55 (3H, s). LCMS (M+H)⁺ m/z 542 (t = 1.28 min.).

Ejemplo 564



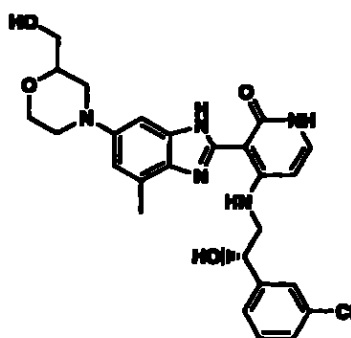
4-[2-(7-Bromo-2,3-dihidro-benzofurano-5-il)-(S)-2-hidroxi-etilamino]-3-(6-[(R)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridina-2-ona y 4-[2-(7-bromo-2,3-dihidro-benzofurano-5-il)-(S)-2-hidroxi-

~~474~~
474

etilamino]-3-{6-[(S)-2-fluorometil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridina-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.26 - 7.40 (4H, m), 7.19 (1H, s), 6.24 (1H, d, J = 7.6 Hz), 4.81 - 4.82 (1H, m), 4.49 - 4.61 (4H, m), 3.18 - 4.18 (11H, m), 2.59 (3H, s). LCMS (M+H)⁺ m/z 598 (t = 1.32 min.).

Ejemplo 565

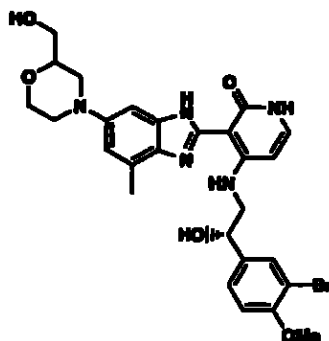


4-[2-(3-Cloro-fenil)-(S)-2-hidroxi-etilamino]-3-{6[(R)-2-hidroxi-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridina-2-ona y 4-[2-(3-cloro-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-hidroxi-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridina-2-ona: ¹H RMN

(400 MHz, CD₃OD) δ 7.49 (1H, s), 7.23 - 7.37 (6H, m), 7.10 (1H, s), 6.24 (1H, d, J = 7.6 Hz), 4.95 - 4.96 (1H, m), 4.19 (1H, m), 3.94 - 4.80 (2H, m), 3.59 - 3.71 (8H, m), 2.63 (3H, s). LCMS (M+H)⁺ m/z 510 (t = 1.21 min.).

475

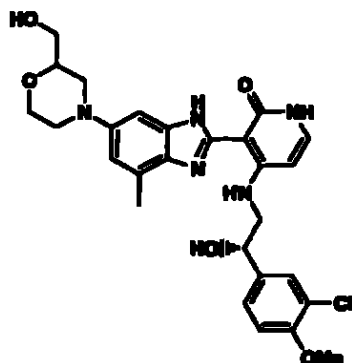
Ejemplo 566



4-[2-(3-Bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6[(R)-2-hidroxi-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridina-2-ona y 4-[2-(3-bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(S)-2-hidroxi-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

^1H NMR (400 MHz, CD_3OD) δ 7.62 (1H, Ang d, $J = 2.0$ Hz), 7.54 (1H, s), 7.29 – 7.36 (3H, m), 6.95 (1H, d, $J = 8.4$ Hz), 6.23 (1H, d, $J = 7.6$ Hz), 4.88 – 4.89 (1H, m), 3.56 – 4.19 (11H, m), 3.80 (3H, s), 2.60 (3H, s). LCMS ($M+H$) $^+$ m/z 584 ($t = 1.16$ min.).

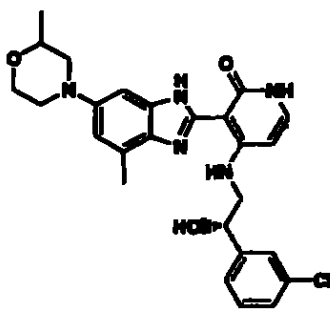
Ejemplo 567



4-[2-(3-Cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-hidroxi-etil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-hidroxi-etil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridina-2-ona:

^1H NMR (400 MHz, CD_3OD) δ 7.68 (1H, s), 7.54 (1H, s), 7.45 (1H, s), 7.39 (1H, s), 7.30 – 7.32 (2H, m), 6.98 (1H, d, $J = 8.4$ Hz), 6.22 (1H, d, $J = 7.6$ Hz), 4.89 (1H, m), 4.11 – 4.19 (3H, m), 3.80 (3H, s), 3.49 – 3.72 (8H, m), 2.60 (3H, s). LCMS ($M+H$) $^+$ m/z 540 ($t = 1.09$ min.).

Ejemplo 568



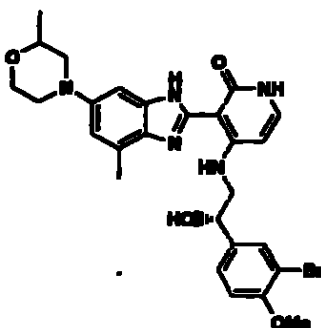
477

4-[2-(3-Cloro-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2{(3-cloro-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD) δ

7.75 (1H, s), 7.48 (1H, s), 7.42 (1H, s), 7.23 – 7.37 (4H, m), 6.24 (1H, d, J = 7.2 Hz), 4.94 – 4.97 (1H, m), 4.11 – 4.16 (3H, m), 3.61 – 3.68 (5H, m), 3.38 (1H, m), 2.64 (3H, s), 1.29 (3H, d, J = 6.4 Hz). LCMS (M+H)⁺ m/z 494 (t = 1.32 min.).

Ejemplo 569

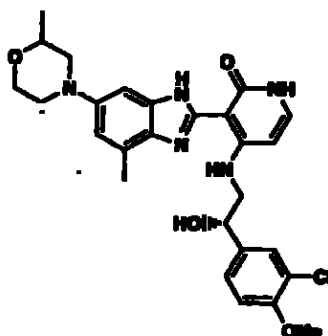


4-[2-(3-Bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-2-{6-[(R)-2-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridina-2-ona:

¹H NMR

(400 MHz, CD₃OD) δ 7.63 (1H, s), 7.62 (1H, s), 7.30 – 7.61 (3H, m), 6.95 (1H, d, *J* = 8.4 Hz), 6.22 (1H, d, *J* = 7.6 Hz), 4.88 – 4.90 (1H, m), 4.08 – 4.18 (3H, m), 3.80 (3H, s), 3.61 – 3.67 (5H, m), 3.32 – 3.34 (1H, m), 2.60 (3H, s), 1.28 (3H, d, *J* = 6.0 Hz).
LCMS (M+H)⁺ *m/z* 568 (*t* = 1.31 min.).

Ejemplo 570

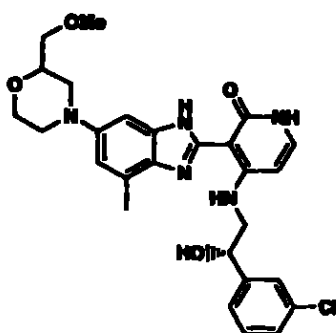


4-[2-(3-Cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridina-2-ona:

¹H NMR

(400 MHz, CD₃OD) δ 7.48 (1H, Ang d, *J* = 2.0 Hz), 7.40 (1H, br s), 7.31 (1H, Ang d, *J* = 2.0 Hz), 7.29 (1H, Ang d, *J* = 2.0 Hz), 6.97 (1H, d, *J* = 8.4 Hz), 6.22 (1H, d, *J* = 7.6 Hz), 4.87 – 4.90 (1H, m), 4.11 (1H, m), 3.95 – 4.01 (2H, m), 3.80 (3H, s), 3.47 (4H, m), 3.32 (1H, m), 3.25 (1H, m), 2.57 (3H, s), 1.27 (3H, d, *J* = 6.4 Hz).
LCMS (M+H)⁺ *m/z* 525 (*t* = 1.27 min.).

Ejemplo 571

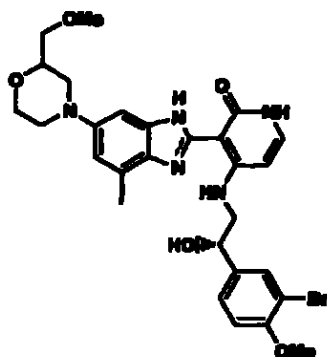


4-[2-(3-Cloro-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-metoximetil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-cloro-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-metoxi-metil-morfolina-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-ona:

¹H NMR

(400 MHz, CD₃OD) δ 7.49 (1H, Ang d, J = 2.0 Hz), 7.23 – 7.36 (6H, m), 6.22 (1H, d, J = 7.2 Hz), 4.93 – 4.96 (1H, m), 4.08 – 4.21 (11H, m), 3.38 (3H, s), 2.60 (3H, s), 1.27 (3H, d, J = 6.4 Hz). LCMS (M+H)⁺ m/z 524 (t = 1.35 min.).

Ejemplo 572

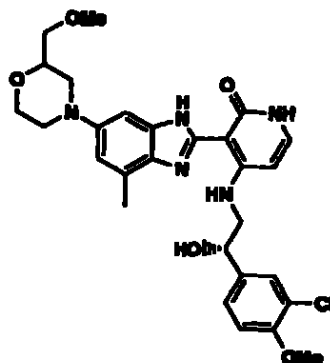


480

4-[2-(3-Bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-ona y 4-[2-(3-bromo-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(S)-2-metoximetil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.63 (1H, Ang d, J = 2.0 Hz), 7.40 (1H, br s), 7.30–7.36 (3H, m), 7.19 (1H, br s), 6.95 (1H, d, J = 8.4 Hz), 6.23 (1H, d, J = 7.2 Hz), 4.87–4.89 (1H, m), 4.18 (1H, m), 3.97–4.03 (3H, m), 3.80 (3H, s), 3.54–3.66 (7H, m), 3.39 (3H, s), 2.59 (3H, s). LCMS (M+H)⁺ m/z 598 (t = 1.31 min.).

Ejemplo 573

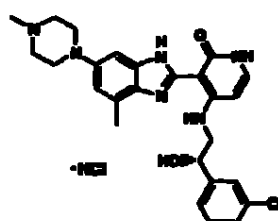


4-[2-(3-Cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamina]-3-{6-[(R)-2-metoximetil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona y 4-[2-(3-cloro-4-metoxi-fenil)-(S)-2-hidroxi-etilamino]-3-(6-[(S)-2-metoximetil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona:

481

^1H NMR (400 MHz, CD_3OD) δ 7.52 (1H, s), 7.46 (1H, Ang d, $J = 1.6$ Hz), 7.29–7.34 (3H, m), 6.99 (1H, d, $J = 8.4$ Hz), 6.24 (1H, d, $J = 7.2$ Hz), 4.89 (1H, m), 4.06–4.17 (3H, m), 3.81 (3H, s), 3.54–3.68 (8H, m), 3.38 (3H, s), 2.60 (3H, s).
LCMS ($\text{M}+\text{H}$) $^+$ m/z 554 ($t = 1.28$ min.).

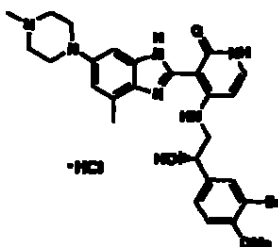
Ejemplo 574



4-[2-(3-Cloro-fenil)-2(S)-hidroxi-etilamino]-3-[4-metil-6-(4-metil-piperacina-1-il)-1H-benzoimidazol-2-il]-1H-piridin-2-ona:

^1H NMR (400 MHz, CD_3OD) δ 7.46 (1H, s), 7.24–7.36 (m, 4H), 7.04 (2H, s), 6.22 (1H, d, $J = 7.64$ Hz), 4.89 (1H, m), 3.30–3.82 (10H, m) 2.97 (3H, s), 2.57 (3H, s). LCMS ($\text{M}+\text{H}$) $^+$ m/z 493 ($t = 1.56$ min.)

Ejemplo 575

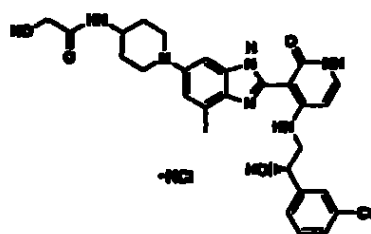


482

ml de MeOH es enfriada a 0°C. luego aproximadamente 10 equivalentes de base Huenigs y aproximadamente 3 equivalentes de ácido clorhídrico son agregadas. El frasco es agitado una vez y se le permitió permanecer a temperatura ambiente por una hora. La evaporación de volátiles y la purificación por prep: HPLC da los compuestos 4-ácido-aminopiperidina.

¹H NMR (500 MHz, CD₃OD) δ 8.06 (1H, s), 7.68 (1H, s), 7.49 (1H, s), 7.44 (1H, d, J = 7.6), 7.27 – 7.38 (4H, m), 6.33 (1H, d, J = 7.6 Hz), 4.96 (1H, dd, J = 4.1, 7.6 Hz), 4.17 (1H, m), 3.87 (4H, m), 3.65 (1H, dd, J = 4.2, 14 Hz), 3.58 (1H, dd, J = 7.8, 13.8 Hz), 2.72 (3H, s), 2.31 (2H, m), 2.19 (2H, m), 2.02 (3H, s). LCMS (M+H)⁺ m/z 535 (t = 1.03 min, YMC Xterra C18 S7 3.0 x 50 mm; Gradiente 0-100% durante 1,5 minutos; índice de flujo 5 ml/min)

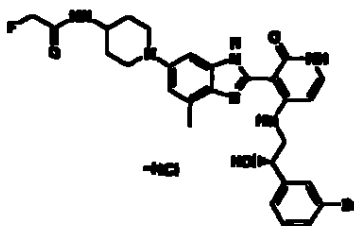
Ejemplo 577



4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-hidroxiacetamido)-piperidin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

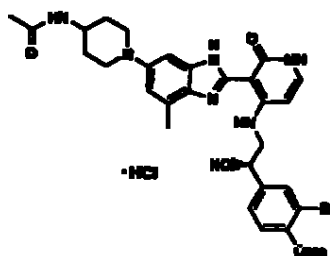
483

LCMS (M + H)⁺ m/z 551 (t = 1,27 min). HPLC t = 5,01 min,
Waters Xterra C18 S5 4,6 x 30 mm; gradiente de 0 - 100%
durante 12 minutos; índice de flujo 5 ml/min

Ejemplo 578

4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-[4-(2-
fluoroacetamido)-piperidin-1-il]-4-metil-1H-
benzoimidazol-2-il)-1H-piridin-2-ona:

LCMS (M + H)⁺ m/z 597 (t = 1,31 min). HPLC t = 6,90 min,
YMC-Pack ODS-A 3,0 x 50 mm, gradiente de 0 - 100% durante
12 minutos; índice de flujo 2,5 ml/min

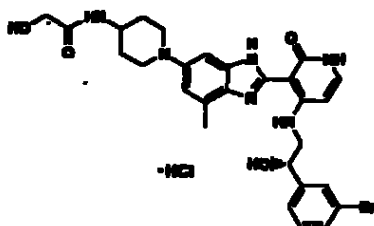
Ejemplo 579

484

4-[2-(3-Bromo-4-metoxi-fenil-2-hidroxi-etilamino)-3-(6-4(acetamido)-piperidin-1-il]-4-metil-1H-benzoimidazol-2-il]-1H-piridin-2-ona:

LCMS (M + H)⁺ m/z 609 (t = 1,27 min). HPLC t = 5,00 min, Waters Xterra C18 S5 4,6 x 30 mm; gradiente de 0 - 100% durante 12 minutos; índice de flujo 5 ml/min

Ejemplo 580

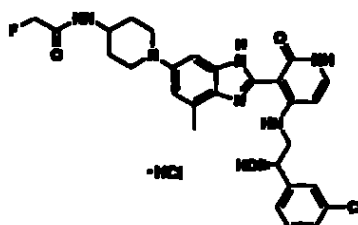


4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-3-(6-[4-(2-hidroxiacetamido)-piperidin-1-il]-4-metil-1H-benzoimidazol-2-il]-1H-piridin-2-ona:

LCMS (M + H)⁺ m/z 595 (t = 1,30 min). HPLC t = 5,09 min, Waters Xterra C18 S5 4,6 x 30 mm; gradiente de 0 - 100% durante 12 minutos; índice de flujo 5 ml/min

Ejemplo 581

485



4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-fluoroacetamido)-piperidin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

LCMS (M + H)⁺ m/z 553 (t = 1,35 min). HPLC t = 5,90 min, YMC-Pack ODS-A 3,0 x 50 mm, gradiente de 0 - 100% durante 10 minutos; índice de flujo 2,5 ml/min

Los siguientes ejemplos (582-584) fueron preparados de acuerdo al esquema VII y III e ilustra la carbonilación de un derivado 4-amino-piperidin

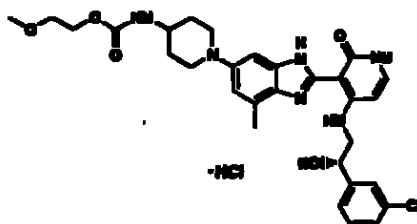
Procedimiento general para los ejemplos 582-584

Una solución del compuesto de 4-amino-piperidina (aproximadamente 50 a 100 umoles) en 5 ml de MeOH es enfriado a 0°C. Luego se agregan aproximadamente 10 equivalentes de base Huenigs y aproximadamente 3 equivalentes de cloruro de carbamoilo. El frasco es agitado una vez y se le permite permanecer a temperatura

486

ambiente durante la noche. La evaporación de volátiles y la purificación por prep. HPLC da los compuestos 4-carbamoyl-aminopiperidina.

Ejemplo 582



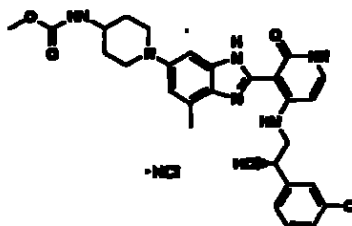
4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-metoxietoxicarbamoil)-piperidin-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridin-2-ona:

$^1\text{H NMR}$ (500 MHz, CD_3OD) δ 7.90 (1H, s), 7.26–7.52 (6H, m), 6.29 (1H, d, $J = 7.5$ Hz), 4.97 (1H, dd, $J = 4.1, 7.0$ Hz), 4.20 (2H, m), 3.93 (1H, m), 3.60–3.84 (8H, m), 3.37 (3H, s), 2.69 (3H, s), 2.33 (2H, m), 2.13 (2H, m).

LCMS $(\text{M} + \text{H})^+$ m/z 595 ($t = 1.09$ min), YMC Xterra C18 S7 3,0 x 50 mm, gradiente de 0 – 100% durante 10 minutos; índice de flujo 5 ml/min

487

Ejemplo 583



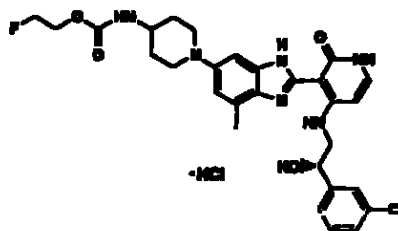
4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(metoxicarbamoil)-piperidin-1-il]-4-metil-1H-benzoiminidazol-2-il}-1H-piridin-2-ona:

¹H NMR

(500 MHz, CD₃OD) δ 8.00 (1H, s), 7.63 (1H, s), 7.26 – 7.49 (5H, m), 6.32 (1H, d, *J* = 7.6 Hz), 4.96 (1H, dd, *J* = 4.2, 7.6 Hz), 3.93 (1H, m), 3.79 – 3.88 (4H, m), 3.67 (3H, s), 3.56 – 3.65 (2H, m), 2.71 (3H, s), 2.32 (2H, m), 2.17 (2H, m).

LCMS (M + H)⁺ *m/z* 551 (*t* = 1,07 min), YMC Xterra C18 S7 3,0 x 50 mm, gradiente de 0 ~ 100% durante 1,5 minutos; índice de flujo 5 ml/min

Ejemplo 584



~~488~~

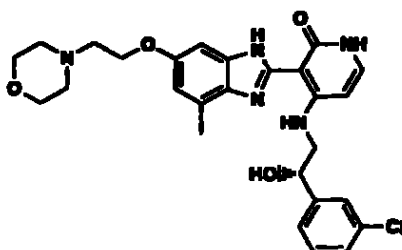
4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-{6-[4-(2-fluoroetoxicarbamoil)-piperidina-1-il]-4-metil-1H-benzoimidazol-2-il}-1H-piridina-2-ona:

¹H NMR (500 MHz, CD₃OD) δ 7.92 (1H, s), 7.26–7.54 (6H, m), 6.3 (1H, d, J = 7.5 Hz), 4.97 (1H, dd, J = 4.5, 7.5 Hz), 4.63 (1H, ^{Ampl} s), 4.53 (1H, d, J = 2.5 Hz), 4.32 (1H, ^{Ampl} s), 4.27 (1H, ^{Ampl} s), 3.93 (1H, m), 3.79–3.85 (4H, m), 3.58–3.72 (2H, m), 2.70 (3H, s), 2.33 (2H, m), 2.15 (2H, m). LCMS (M+H)⁺ m/z 583 (t = 1.29 min,

YMC Xterra C18 S7 3,0 x 50 mm, gradiente de 0 – 100% durante 2 minutos; índice de flujo 5 ml/min

Los siguientes ejemplos (585-590) fueron preparados de acuerdo al esquema VII y III e ilustran el uso de un alcohol como el nucleófilo en el esquema VII.

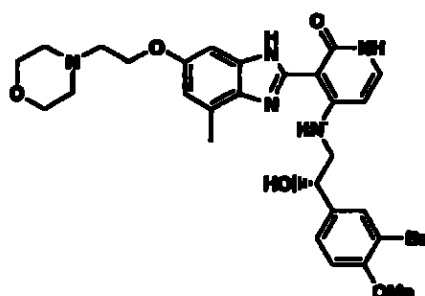
Ejemplo 585 (procedimiento general para ejemplos 585-590)



(s)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(2-morfolin-4-il-etoxi)-1H-benzimidazol-2-il]-1H-piridina-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.53 (1H, s), 7.37–7.39 (1H, m), 7.23–7.30 (3H, m), 7.01 (1H, s), 6.75 (1H, s), 6.21 (1H, d, *J* = 7.2 Hz), 4.98 (1H, t, *J* = 5.6 Hz), 4.40 (2H, br s), 3.97 (4H, br s), 3.45–3.73 (8H, m), 2.54 (3H, s). LCMS (M+H)⁺ *m/z* 524 (*t* = 1.24 min.).

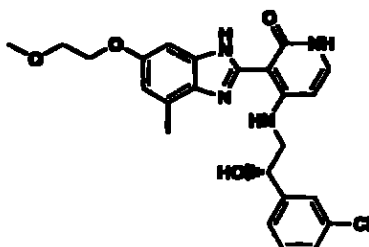
Ejemplo 586



(S)-4-[2-(3-Bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(2-morfolin-4-il-etoxi)-1H-benzimidazol-2-il]-1H-piridina-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.67 (1H, *Ang* d, *J* = 1.6 Hz), 7.36 (1H, dd, *J* = 1.6, 8.4 Hz), 7.25 (1H, d, *J* = 7.2 Hz), 6.98 (1H, s), 6.92 (1H, d, *J* = 8.4 Hz), 6.75 (1H, s), 6.22 (1H, d, *J* = 7.2 Hz), 4.89–4.92 (1H, m), 4.41 (2H, br s), 3.97 (4H, br s), 3.79 (3H, s), 3.34–3.66 (8H, m), 2.51 (3H, s). LCMS (M+H)⁺ *m/z* 598 (*t* = 1.22 min.).

Ejemplo 587

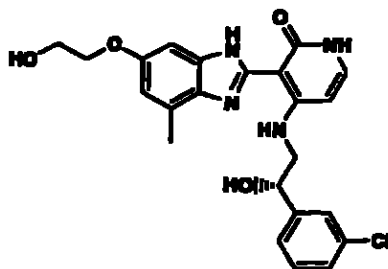


(S)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(2-metoxietoxi)-1H-Benzimidazol-2-il]-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD) δ

7.48 (1H, s), 7.25–7.36 (4H, m), 6.96 (1H, s), 6.81 (1H, s), 6.20 (1H, d, *J* = 7.4 Hz), 4.90–4.93 (1H, m), 4.13–4.14 (2H, m), 3.76–3.77 (2H, m), 3.50–3.61 (2H, m), 3.43 (3H, s), 2.53 (3H, s). LCMS (M+H)⁺ *m/z* 469 (*t* = 1.52 min.).

Ejemplo 588



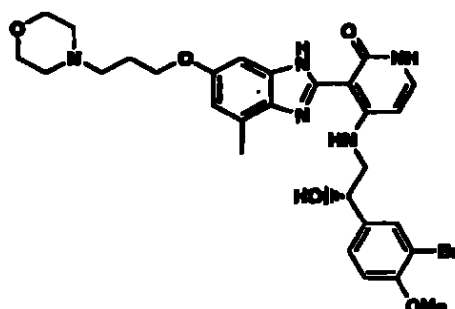
(S)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(2-hidroxi-etoxi)-1H-Benzimidazol-2-il]-1H-piridin-2-ona:

491

¹H NMR (400 MHz, CD₃OD) δ

7.43 – 7.45 (2H, m), 7.27 – 7.34 (3H, m), 7.08 (1H, s), 7.04 (1H, ^{Ang} d, J = 1.0 Hz), 6.28 (1H, d, J = 7.6 Hz), 4.87 (1H, m), 4.13 (2H, t, J = 4.6 Hz), 3.92 (2H, t, J = 4.6 Hz), 3.45 – 3.54 (2H, m), 2.60 (3H, s). LCMS (M+H)⁺ m/z 455 (t = 1.35 min.).

Ejemplo 589



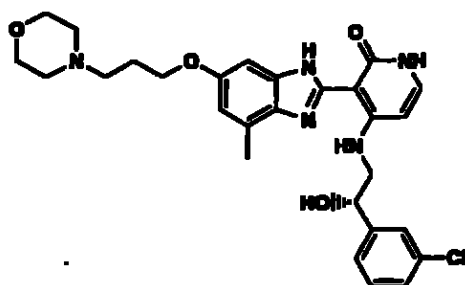
(S)-4-[2-(3-Bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(3-morfolin-4-il-propoxi)-1H-benzimidazol-2-il]-1H-piridina-2-ona:

¹H NMR

(400 MHz, CD₃OD) δ 7.66 (1H, s), 7.35 (1H, dd, J = 1.6, 7.9 Hz), 7.25 (1H, br s), 6.93 (1H, s), 6.91 (1H, s), 6.68 (1H, s), 6.19 (1H, br s), 4.86 (1H, m), 4.05 – 4.10 (4H, br s), 3.79 (3H, s), 3.17 – 3.73 (12H, m), 2.50 (3H, s). LCMS (M+H)⁺ m/z 612 (t = 1.16 min.).

Ejemplo 590

492

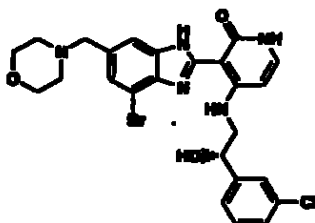


(S)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(3-morfolina-4-il-propoxi)-1H-Benzimidazol-2-il]-1H-piridin-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.52 (1H, s), 7.36 – 7.38 (1H, m), 7.23 – 7.30 (3H, m), 6.92 (1H, s), 6.67 (1H, s), 6.18 (1H, d, *J* = 6.9 Hz), 4.96 (1H, t, *J* = 5.9 Hz), 4.04 – 4.08 (4H, m), 3.82 (2H, m), 3.56 – 3.65 (8H, m), 3.15 – 3.18 (2H, m), 2.52 (3H, s). LCMS (M+H)⁺ *m/z* 538 (*t* = 1.19 min.).

Los siguientes ejemplos (591-593) fueron preparados de acuerdo a los esquemas VII y III en donde el grupo ciano (esquema IV) es convertido a un aldehído que sobrelleva una reducción con una amina.

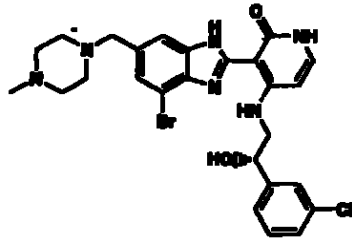
Ejemplo 591 (Procedimiento general para los ejemplos 591-593)



(S)-3-(4-Bromo-6-morfolin-4-ilmetil-1H-benzimidazol-2-il)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-1H-piridina-2-ona: Para una solución de (S)-7-Bromo-2-{4[2-(3-cloro-fenil)-2-hidroxi-etilamino]-2-oxo-1,2-dihidropiridina-3-il}-3H-benzimidazol-5-carbaldehído (130 mg, 0,27 mmol) en metanol (60 ml) fue agregada morfolina (0,2 ml, exceso). La reacción mezclada fue agitada 1 hora a temperatura ambiente. Luego se agregó NaCNBH₃ (1M THF solución, 1,35 ml, 1,35 mmol). La reacción mezclada fue agitada a temperatura ambiente durante la noche y concentrada en vacío. El residuo fue purificado por prep. HPLC para proporcionar todo el compuesto titulado (68 mg, 45%).

¹H NMR (400 MHz, CD₃OD) δ 7.83 (1H, s), 7.69 (1H, s), 7.68 (1H, s), 7.24 - 7.54 (4H, m), 6.30 (1H, d, J = 7.6 Hz), 4.89 - 5.02 (1H, m), 4.50 (2H, s), 3.66 - 3.71 (4H, m), 3.17 - 3.43 (6H, m). LCMS (M+H)⁺ m/z 558 (t = 1.41 min.).

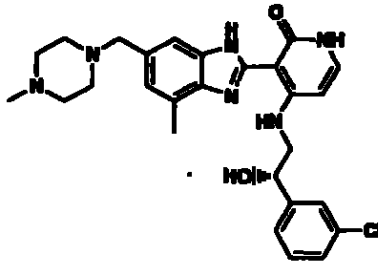
Ejemplo 592



(S)-3-(4-Bromo-6-(4-metil-piperacin-1-ilmetil)-1H-benzimidazol-2-il)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-1H-piridina-2-ona:

¹H NMR (400 MHz, CD₃OD) δ 7.70 (1H, s), 7.55 (2H, s), 7.42 (1H, d, *J* = 7.6 Hz), 7.24 - 7.32 (3H, m), 6.22 (1H, d, *J* = 7.6 Hz), 5.01 (1H, t, *J* = 6.2 Hz), 4.35 (2H, br s), 3.48 - 3.71 (10H, m), 2.98 (3H, s). LCMS (*M*+H)⁺ *m/z* 571 (*t* = 1.37 min.).

Ejemplo 593



(S)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[4-metil-6-(4-metil-piperazin-1-ilmetil)-1H-Benzimidazol-2-il]-1H-piridin-2-ona: Mediante una mezcla de (S)-3-(4-Bromo-6-(4-metil-piperacin-1-ilmetil)-1H-benzimidazol-2-il)-4-[2-(3-cloro-fenil)-2-hidroxi-etilamino]-1H-piridina-2-ona (80

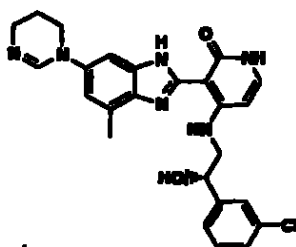
495

mg, 0,14 mmol), tetrametil estaño (2,5) ml, exceso), PdCl₂(PPh₃)₄ (10 mg, 0,014 mmol), y KF (40mg, 0,7 mmol) en DMF (2 ml) en un frasco se hizo burbujear Nitrógeno, se selló, y se calentó a 100°C por dos días. La reacción mezclada fue pasada por una almohadilla pequeña de celita. Después de la concentración, el residuo fue purificado por prep, HPLC para dar el compuesto titulado (34 mg, 48 %).

¹H NMR (400 MHz, CD₃OD) δ 7.53 (1H, s), 7.45 (1H, s), 7.24 - 7.40 (4H, m), 7.09 (1H, s), 6.22 (1H, d, J = 7.6 Hz), 4.99 (1H, t, J = 6.4 Hz), 4.04 (2H, br s), 3.61 - 3.74 (2H, m), 2.98 - 3.34 (8H, m), 2.80 (3H, s), 2.58 (3H, s).
LCMS (M+H)⁺ m/z 507 (t = 1.29 min.).

Los siguientes ejemplos (594-595) fueron preparados de acuerdo a los esquemas VII y III e ilustran el uso del tetrahidropirimidina como el nucleófilo en el esquema VII.

Ejemplo 594



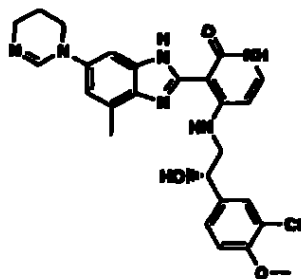
D496

4-[2-(3-Cloro-fenil)-2 (S)-hidroxi-etilamino]-3-[4-metil-6-(1,4,5,6-tetrahidropirimidina-1-il)-1H-benzoimidazol-2-il]-1H-piridina-2-ona:

¹H

NMR (400 MHz, CD₃OD) δ 8.38 (1H, s), 7.52 (1H, s), 7.21-7.41 (5H, m), 7.04 (1H, d, J = 1.2 Hz), 6.21 (1H, d, J = 7.6 Hz), 4.97 (1H, t, J = 4.9 Hz), 3.97 (2H, m), 3.60-3.73 (2H, m), 3.52 (2H, t, J = 5.74 Hz), 2.60 (3H, s), 2.25 (2H, m) LCMS (M+H)⁺ m/z 477 (t = 1.79 min.)

Ejemplo 595



4-[2-(4-Metoxi-3-cloro-fenil)-2 (S)-Hidroxi-etilamino]-3-[4-metil-6-(1,4,5,6-tetrahidropirimidina-1-il)-1H-benzoimidazol-2-il]-1H-piridina-2-ona:



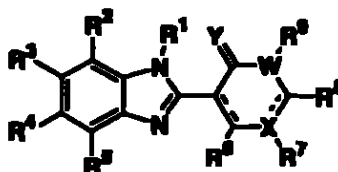
¹H NMR (400 MHz, CD₃OD) δ 8.37 (1H, s), 7.52 (1H, s), 7.04-7.52(4H, m), 7.04 (1H, d, *J* = 1.2 Hz), 6.21 (1H, d, *J* = 7.6 Hz), 4.98 (1H, t, *J* = 4.92 Hz) 3.97 (5H, m) 3.60-3.73 (2H, m), 3.52 (2H, t, *J* = 5.74 Hz), 2.60 (3H, s), 2.26 (2H, m). LCMS (M+H)⁺ *m/z* 507 (*t* = 1.67 min.)

Es de entender que los ejemplos descritos anteriormente no sirven para limitar el verdadero alcance de esta invención, si no que son presentados con fines ilustrativos. Todas las referencias citadas aquí se incorporan como referencia en su totalidad.

498

REIVINDICACIONES:

1. Un compuesto de acuerdo con la fórmula I



I

Sus enantiómeros, diastereómeros, sales farmacéuticamente aceptables, hidratos, prodrogas y solvatos de estos;

En donde

X se selecciona del grupo que consiste de N, C, alquilo C₁-C₃, alquilo C₁-C₃ sustituido con uno o más R⁷, y un enlace directo;

Y se selecciona del grupo que consiste de O y S;

W se selecciona del grupo que consiste de N, C, O, y S, siempre que cuando W sea O o S, R⁹ este ausente;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, son cada uno independientemente seleccionados del grupo que consiste de H, alquilo C₁-C₆, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, halo, amino, OR⁶⁰, NO₂, OH, SR⁶⁰, NR⁶⁰R⁶¹, CN, CO₂R⁶⁰, CONR⁶⁰R⁶¹, CO₂NR⁶⁰R⁶¹, NR⁶²CONR⁶⁰R⁶¹,

244
499

$\text{NR}^{60}\text{SO}_2\text{R}^{61}$, $\text{SO}_2\text{NR}^{60}\text{R}^{61}$, $\text{C}(\text{NR}^{62})\text{NR}^{60}\text{R}^{61}$, arilo, heteroarilo,
 $(\text{CH}_2)_n\text{OR}^{60}$, $(\text{CH}_2)_n\text{NR}^{60}\text{R}^{61}$, $(\text{CH}_2)_n\text{SR}^{60}$, $(\text{CH}_2)_n\text{arilo}$,
 $(\text{CH}_2)\text{heteroarilo}$, $(\text{CH}_2)_n\text{heterocicloalquilo}$, NH-Z-arilo , y
 NH-Z-heteroarilo ;

En donde n es 1 a 3; y

Z se selecciona del grupo que consiste de la cadena alquilo $\text{C}_1\text{-C}^4$, alquenilo, y alquinilo; Z tiene uno o más grupos hidroxil, tiol, alcoxi, tioalcoxi, amino, halo, $\text{NR}^{60}\text{SO}_2\text{R}^{61}$, Z opcionalmente incorpora uno o más grupos seleccionados del grupo que consiste de CO , CNOH , CNOR^{60} , CNNR^{60} , CNNCOR^{60} y $\text{CNNSO}_2\text{R}^{60}$; y

R^{60} , R^{61} , y R^{62} son independientemente seleccionados del grupo que consiste de H , alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, hidroxil, alcoxi, arilo, heteroarilo, heteroarilalquilo, y alquil- R^{25} en donde R^{25} es hidrógeno, alquenilo, hidroxil, tiol, alcoxi, tioalcoxi, amino, alquilamino, dialquilamino, arilo, heteroarilo, ciano, halo, sulfoxil, sulfonilo, $-\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}\text{C}(\text{O})\text{R}^{31}$, $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $-\text{C}(\text{O})\text{NR}^{30}\text{R}^{31}$, heteroarilo o heterocicloalquilo, y

R^{30} y R^{31} son, independientemente, hidrogeno, alquilo, cicloalquilo, o alquil- R^{25} .

2. El compuesto de acuerdo a la reivindicación 1 en donde

R^1 , R^7 , R^8 , y R^9 son H;

R^2 y R^4 son H o F;

Y es O;

X se selecciona del grupo que consiste de N y CH;

W es N;

R^5 se selecciona del grupo que consiste de H, metilo, etilo, isopropilo, butilo secundario, ciclopropilo, F, y CF^3 ;

R^6 se selecciona del grupo que consiste de H, 2-aminometilpiridina, $NHCH_2CH(OH)Ph$, $NHCH_2CH(OH)(3-Cl-Ph)$, $NHCH_2CH(OH)(3-Br-Ph)$, $NHCH_2CH(OH)(3-Br-4-OMe-Ph)$, $NHCH(CH_2OH)CH_2Ph$, $HCH_2CH(OH)arilo$, y $NHCH(CH_2OH)CH_2 arilo$; y

R^3 se selecciona del grupo que consiste de OR^{60} , $C(NH)NHR^{60}$, $C(O)NHR^{60}$ imidazol, imidazolina, tetrahidropirimidina, pirazina, morfolino, homomorfolino, piperidina, pirrolidina, homopiperazina, y amino; en donde

R^{60} se selecciona del grupo que consiste de H, alquilo, cicloalquilo, heterocicloalquilo, y alquil- R^{25} en donde R^{25} es hidrogeno, alquenilo, hidroxilo, tiol, tioalcoxi,

alcoxi, tioalcoxi, halo, cano, sulfoxi, sulfonilo, -
 $\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}_{30}\text{C}(\text{O})\text{R}^{31}$, $-\text{NR}_{30}\text{SO}_2\text{R}^{31}$, $-\text{C}(\text{O})\text{NR}^{30}\text{R}^{31}$, o un
heteroarilo o heterocicloalquilo; y

R_{30} y R_{31} son, independientemente, hidrógeno, alquilo,
cicloalquilo, o alquil- R^{25} .

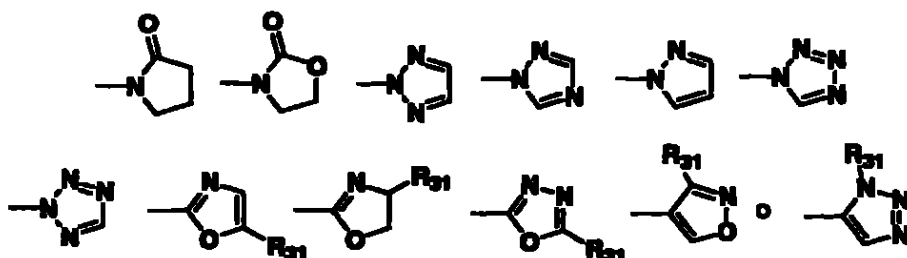
3. El compuesto de acuerdo con la reivindicación 2 en
donde R^3 es $-\text{OR}^{60}$ y R^{60} es alquilo, y alquilo- R^{25} , en
donde

R^{25} es hidrógeno, alquenilo, hidróxido, tiol, alcóxido,
tioalcóxido, amino, halo, ciano, sulfoxi, sulfonilo, -
 $\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}(\text{O})\text{R}^{31}$, $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $-\text{C}(\text{O})\text{NR}^{30}\text{R}^{31}$, heteroarilo
o heterocicloalquilo; y

R^{30} y R^{31} son, independientemente, hidrógeno, alquilo,
cicloalquilo, o alquilo- R^{25} .

4. El compuesto de acuerdo con la reivindicación 3 en
donde R^{60} es metil, $-(\text{CH}_2)_n\text{CH}_2\text{OH}$, o $-(\text{CH}_2)_n\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2$
O, y n es 0, 1, o 2.

5. El compuesto de acuerdo a la reivindicación 3 en donde
 R^{25} es morfolina,



En donde R^{33} es hidrógeno, alquilo, o alquilo sustituido.

6. El compuesto de acuerdo a la reivindicación 2 en donde R^3 es piperacina, homopiperacina, 3-metilpiperazina, o 3,5-dimetilpiperazina siendo opcionalmente sustituida en la posición 4-N con un compuesto seleccionado de el grupo consistiendo de, alquilo, cicloalquilo, alquil- R^{25} , $-C(O)-R^{15}$, o CO_2R^{15} en donde R^{15} es hidrógeno, alquil, arilo, alquil- R^{25} , amino o arilo; y

R^{25} es hidrógeno, alquenilo, hidroxilo, tiol alcoxi, tioalcoxi, amino, alquilamino, dialquilamino, ciano, halo, sulfoxi, sulfonilo, arisulfonil, $NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o heterocicloalquil; y

R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo o alquilo- R^{25} .

7. El compuesto de acuerdo con la reivindicación 6 en donde dicha piperazina es sustituida con metil, etilo, CH_2 -ciclopropilo, hidroxietilo, 2-dimetilaminoetilo, 2-dietilaminoetilo, 2-aminoetilo, 2-metilaminoetilo, 2-etilaminoetilo, metoxietilo, etoxietilo, morfolina, y morfolinetilo.

8. El compuesto de acuerdo a la reivindicación 2 en donde R^3 es un grupo amino seleccionado a partir del grupo que consiste de hidroxialquilamino, aminoalquilamino, dialquilaminoalquilamino, y heterocicloalquilalquilamino.

9. El compuesto de acuerdo a la reivindicación 8 en donde dicho amino se selecciona del grupo que consiste de $\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{NMeCH}_2\text{CH}_2\text{OH}$, $\text{NEtCH}_2\text{CH}_2\text{OH}$, $\text{NHCH}_2\text{CH}_2\text{NH}_2$, $\text{NMeCH}_2\text{CH}_2\text{NH}_2$, $\text{NEtCH}_2\text{CH}_2\text{NH}_2$, $\text{NHCH}_2\text{CH}_2\text{NMe}_2$, $\text{NMeCH}_2\text{CH}_2\text{NMe}_2$, $\text{NEtCH}_2\text{CH}_2\text{NMe}_2$, $\text{NHCH}_2\text{CH}_2\text{NEt}_2$, $\text{NMeCH}_2\text{CH}_2\text{Net}_2$, $\text{NEtCH}_2\text{CH}_2\text{NEt}_2$, $\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$, $\text{NMeCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$, $\text{NEtCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$.

10. El compuesto de acuerdo a la reivindicación 2 en donde R^3 es piperidina, opcionalmente sustituida con hidroxil, tiol, amino, alquilamino, dialquilamino, alcoxi, tioalcoxi, 1,3 dioxolano, 1,3 dioxano, -

77
504

NHC(O)R^{15} , $\text{NHC(O)}_2\text{R}^{15}$, en donde R^{15} es hidrógeno, alquilo, arilo o alquilo- R^{25} en donde R^{25} es Hidrógeno, alquenoilo, hidroxilo, tiol, alcoxi, tioalcoxi, amino, halo, ciano, sulfoxilo, sulfonilo, $-\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}\text{C(O)R}^{31}$, $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $\text{C(O)NR}^{30}\text{R}^{31}$, heteroarilo o heterocicloalquilo; y

R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo, o alquilo- R^{25} .

11. El compuesto de acuerdo a la reivindicación 2 en donde R^3 es morfolina, tiomorfolina, sulfoximorfolina, sulfonilmorfolina, o homomorfolina, o una morfolina sustituida, tiomorfolina, sulfoximorfolina, sulfonilmorfolina, o homomorfolina.

12. El compuesto de acuerdo a la reivindicación 11 en donde dicha morfolina, tiomorfolina, sulfoximorfolina, sulfonilmorfolina, o homomorfolina es sustituida con hidroxilo, tiol, amino, alquilamino, dialquilamino, alcoxi, tioalcoxi, alquil- R^{25}

$-\text{NHC(O)R}^{15}$, $-\text{NHCO}_2\text{R}^{15}$, en donde R^{15} es hidrógeno, alquilo, arilo o alquilo- R^{25} en donde R^{25} es hidrógeno, alquenoilo, hidroxilo, tiol, alcoxi, tioalcoxi, amino, halo, ciano, sulfoxilo, sulfonilo, $-\text{NR}^{30}\text{COOR}^{31}$, $-\text{NR}^{30}\text{C(O)R}^{31}$, $-\text{NR}^{30}\text{SO}_2\text{R}^{31}$, $\text{C(O)NR}^{30}\text{R}^{31}$, heteroarilo o heterocicloalquilo; y



R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo, o alquilo- R^{25} .

13. El compuesto de acuerdo a la reivindicación 2 en donde R^3 es $(CH_2)_n$ -morfolina o $(CH_2)_n$ -piperazina, en donde n es 1 a 3.

14. El compuesto de acuerdo a la reivindicación 2 en donde R^3 es un N- tetrahidropirimidina o N-iminidazolina opcionalmente sustituidos.

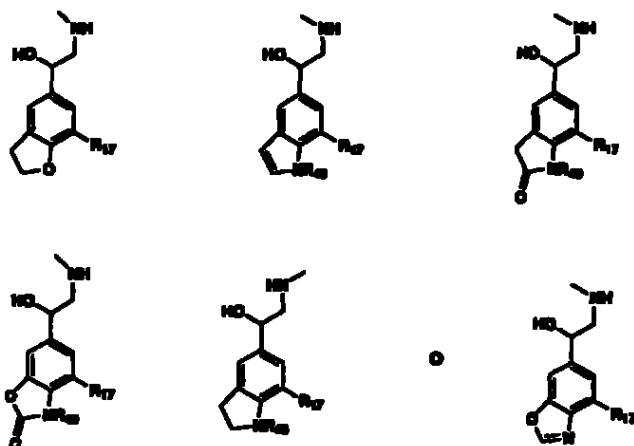
15. El compuesto de acuerdo a la reivindicación 14 en donde por lo menos uno de dichos sustituyentes es alquilo, hidroxialquilo, alcoxialquilo, haloalquilo, cianoalquilo, carboxilo, o carboxamida.

16. El compuesto de acuerdo con la reivindicación 2 en donde R^3 es pirrolidina.

17. El compuesto de acuerdo con la reivindicación 2 en donde dicha pirrolidina es seleccionada a partir del grupo que consiste de 3- hidroxilpirrolidina, 3- alcoxipirrolidina, y 3- alquilamino pirrolidina, 3- dialquilamino pirrolidina.

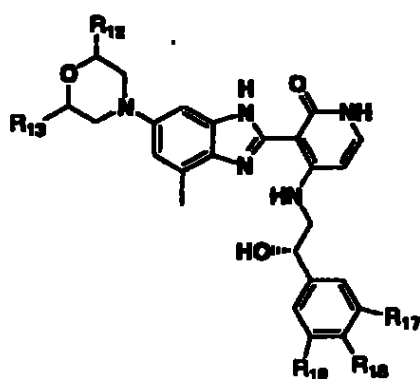
18. El compuesto de acuerdo a la reivindicación 2 en donde R⁶ es seleccionada a partir de el grupo que consiste de H, 2-aminometilpiridina, NHCH₂CH(OH)arilo, y NHCH(CH₂OH)CH₂ arilo.
19. El compuesto de acuerdo a la reivindicación 18 en donde dicho arilo es un fenilo opcionalmente sustituido.
20. El compuesto de acuerdo a la reivindicación 19 en donde dicho fenilo es sustituido con un Br, Cl, F, Alcoxi o NHSO₂CH₃.
21. El compuesto de acuerdo con la reivindicación 19 en donde dicho sustituyente es 3-Br, 3-Cl o 3-F.
22. El compuesto de acuerdo con la reivindicación 19 en donde dicho sustituyente es 4-F o 4-metoxi.
23. El compuesto de acuerdo con la reivindicación 19 en donde R⁶ es

507



En donde R^{17} es H, Br, Cl, o F y R^{40} es H o alquilo.

24. Un compuesto teniendo la fórmula:



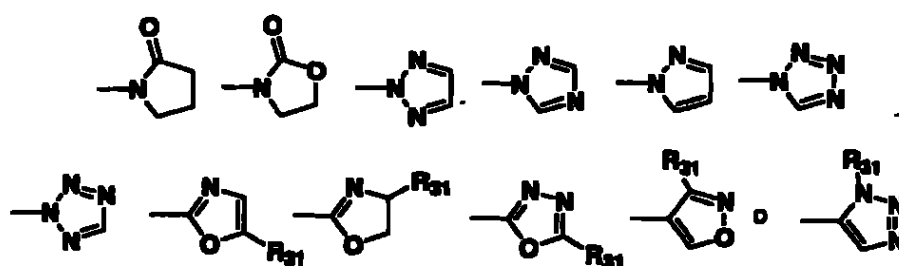
En donde R^{12} y R^{13} son, independientemente, hidrógeno, alquilo o alquilo- R^{25} en donde R^{25} es hidrógeno, hidroxí, tiol, alquenilo, amino, alcoxi, tioalcoxi, halo, ciano, sulfoxi, sulfonil, $-CO_2H$, $-C(O)NR^{30}R^{31}$, $-NR^{30}SO_2R^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}C(O)OR^{31}$, heteroarilo o heterocicloalquilo;

R^{17} , R^{18} y R^{19} son, independientemente, hidrógeno, halógeno, o alcoxi, o R^{18} y R^{19} juntos forman un grupo

508

heterocicloalquilo o heteroarilo; y R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, o alquilo- R^{25} .

25. El compuesto de acuerdo con la reivindicación 24 en donde R^{25} es morfolina,

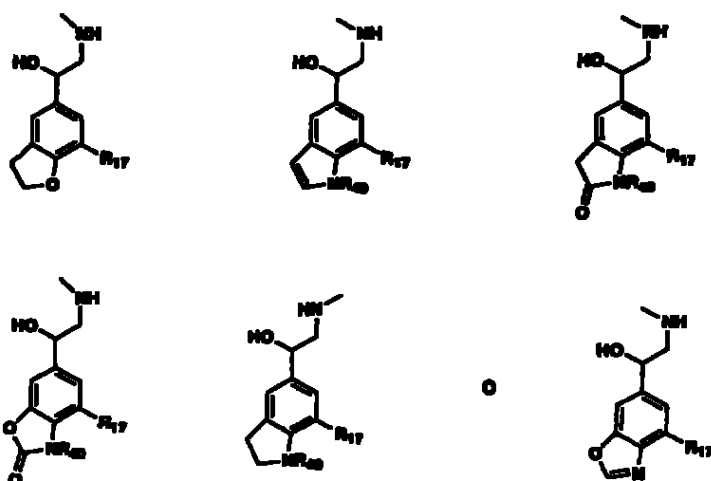


En donde R^{33} es hidrógeno, alquilo o un alquilo sustituido.

26. El compuesto de acuerdo a la reivindicación 24 en donde R^{12} es hidrógeno, metil, hidroximetil, metoximetil, CH_2F , CH_2CN , CO_2H , o $COONR^{30}$ R^{31} en donde R^{30} y R^{31} son, independientemente, hidrógeno, o alquilo- R^{25} .

27. El compuesto de acuerdo con la reivindicación 24 que incorpora la cadena lateral

309

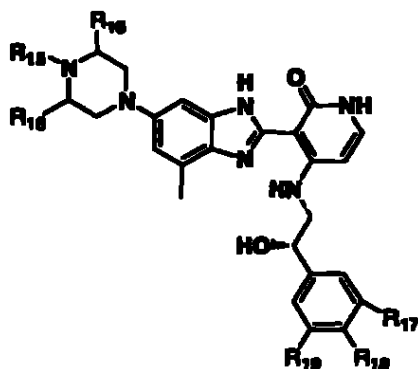


En donde R^{10} es hidrógeno, y R^{70} es hidrógeno o halógeno.

28. El compuesto acuerdo a la reivindicación 24 en donde R^{12} y R^{13} son H; R^{17} es Br, F, o Cl; R^{18} es metoxi o fluoro; y R^{19} es H; o R^{18} y R^{19} juntos forman 4-0,5 dihidrofuranilo.

29. El compuesto acuerdo a la reivindicación 24 en donde R^{12} y R^{13} son metilo; R^{17} es Br, F, o Cl, R^{18} es hidrógeno o metoxi; y R^{19} es H.

30. Un compuesto que tiene la fórmula



En donde R^{15} es hidrógeno, alquilo, o alquilo- R^{25} , en donde R^{25} es hidrógeno, hidroxilo, tiol, alqueno, amino, alcoxi, tioalcoxi, halo, ciano, sulfoxi, sulfonilo,

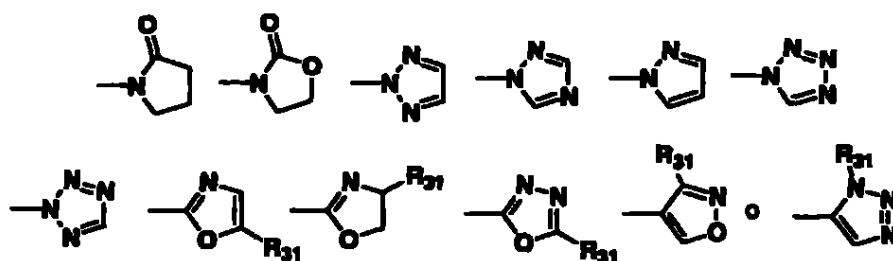
$-NR^{30}COOR^{31}$, $-NR^{30}C(O)^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o heterocicloalquilo;

R^{16} es cada uno independientemente hidrógeno o metilo;

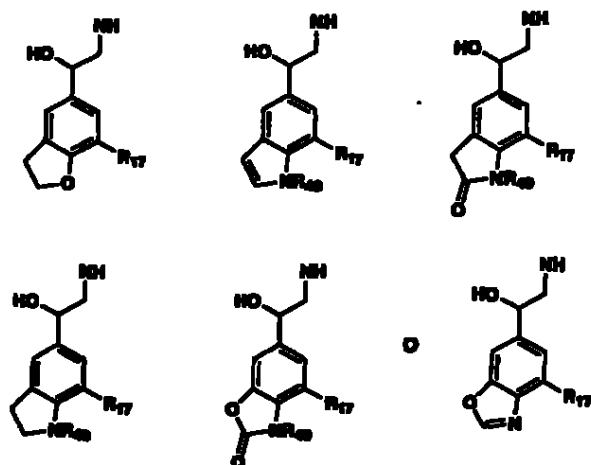
R^{17} , R^{18} y R^{19} son, independientemente, hidrógeno, halógeno, o alcoxi; o R^{18} y R^{19} juntos forman un grupo heterocicloalquilo o heteroarilo; y R^{30} y R^{31} son, independientemente, hidrógeno, alquilo o alquilo- R^{25} .

31.El compuesto acuerdo a la reivindicación 30 en donde R^{25} es morfolina, tiomorfolina,

511



32. El compuesto de acuerdo con la reivindicación 30 que incorpora la cadena lateral



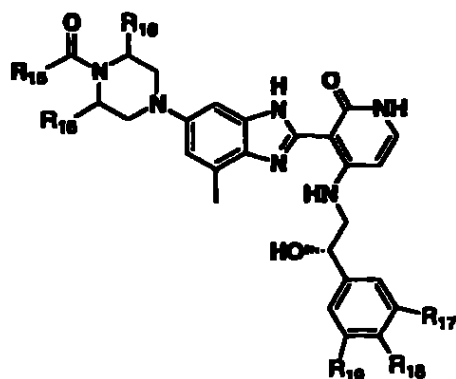
En donde R^{40} es hidrógeno o alquilo y R^{17} es hidrógeno o halógeno.

33. El compuesto de acuerdo con la reivindicación 30 en donde R^{15} es hidrógeno, metil, etil o

$(CH_2)_nCH_2-R^{25}$ en donde R^{25} es OH, OMe, F, CN, CF_3 , $SOCH_3$, o SO_2CH_3 en donde n es 0 o 1.

34. El compuesto acuerdo a la reivindicación 30 donde R^{15} es cianoetil, hidroxietil, $CH_2CH_2SOCH_3$, $CH_2CH_2CH_2F$, CH_2CH_2CN , o $CH_2CH_2CF_3$; R^{16} y R^{19} son H; R^{17} es Br, o Cl; y R^{18} es hidrógeno o metoxi.

35. Un compuesto tiene la fórmula:



Donde

R^{15} es hidrógeno, alquilo, arilo o alquilo- R^{25} ;

R^{25} es hidrógeno, hidroxil, tiol, alquenoil, alcóxido, tioalcóxido, amino, halo, ciano, sulfonilo, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SOR^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o heterocicloalquilo;

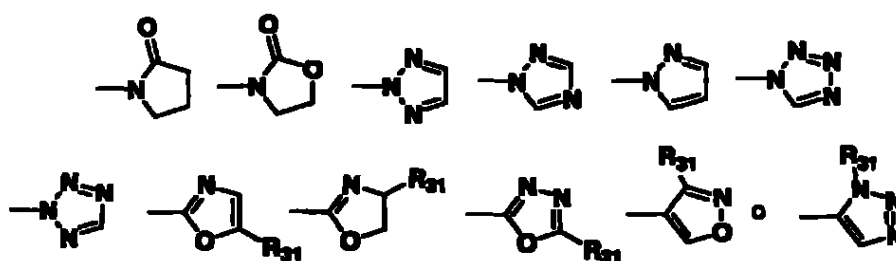
R^{16} es cada uno independientemente hidrógeno o metil;

R^{17} , R^{18} y R^{19} son, independientemente, hidrógeno, halógeno, o alcóxido, o R^{18} y R^{19} juntos forman un grupo heterocicloalquilo o heteroarilo; y

R^{30} y R^{31} son, independientemente, hidrógeno, alquilo, cicloalquilo o alquilo- R^{25} .

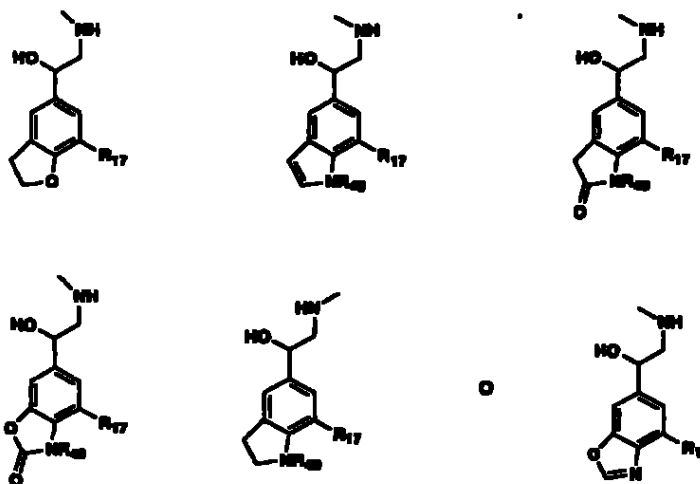
1513

36. Los compuestos de acuerdo a la reivindicación 35 en donde R^{25} es morfolina, tiomorfolina,



En donde R^{33} es hidrógeno, alquilo, o alquilo sustituido.

37. Los compuestos de acuerdo a la reivindicación 35 que incorpora la cadena lateral

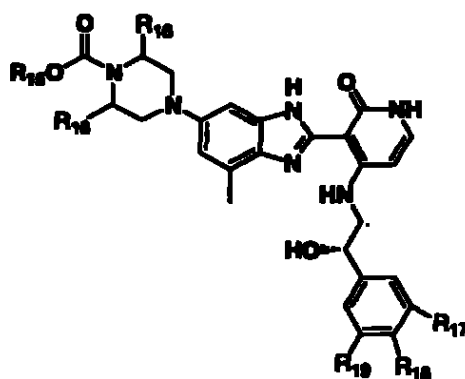


en donde R^{40} es hidrógeno o alquilo y R^{17} hidrógeno o halo.

514

38. El compuesto de acuerdo a la reivindicación 35 en donde R^{15} es hidrógeno o metil; R^{17} es bromo, cloro o flúor; R^{18} es hidrógeno o metoxi; y R^{19} es hidrógeno.

39. Un compuesto tiene la fórmula



En donde

R^{15} es hidrógeno, alquilo, o, alquilo- R^{25} ;

R^{25} es hidrógeno, hidroxil, tiol, alquenoil, alcóxido, tioalcóxido, amino, halo, ciano, sulfonilo, -

$-NR^{30}COOR^{31}$, $-NR^{30}C(O)^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$,

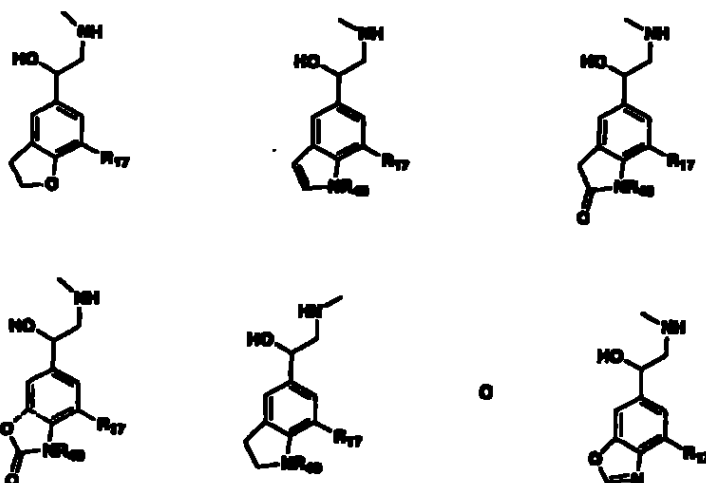
heteroarilo o heterocicloalquilo;

R^{16} es cada uno independientemente hidrógeno o metilo;

R^{17} , R^{18} y R^{19} son, independientemente, hidrógeno, halógeno, o alcoxi; o R^{18} y R^{19} juntos forman un grupo heterocicloalquilo o heteroarilo; y R^{30} y R^{31} son, independientemente, hidrógeno, alquil o alquil- R^{25} .

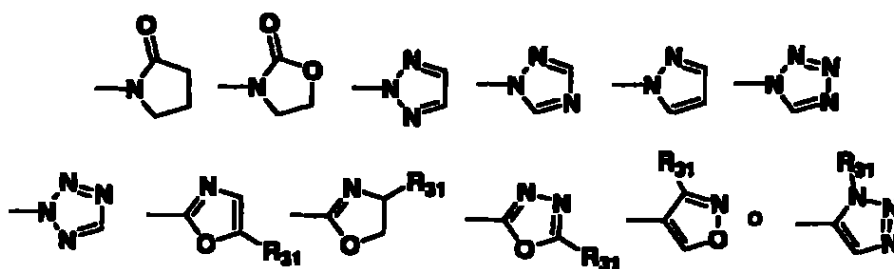
315

40. El compuesto de acuerdo a la reivindicación 39 que incorpora la cadena lateral



En donde R^{40} es hidrógeno o alquilo y R^{17} hidrógeno o halo.

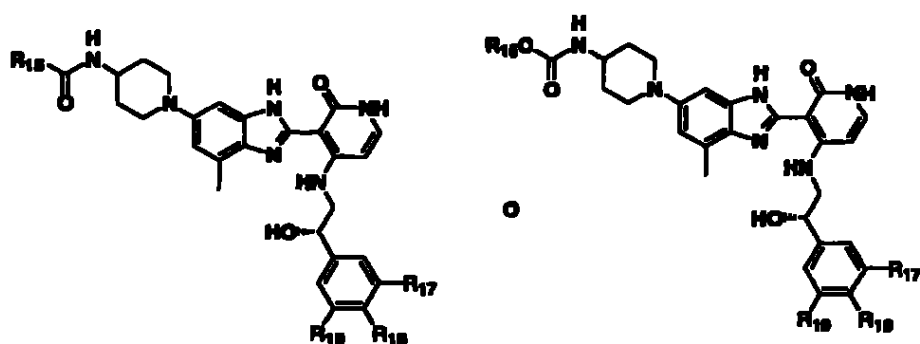
41. El compuesto acuerdo a la reivindicación 39 en donde R^{15} es hidrógeno, metil, etilo, o $-(CH_2)_nCH_2-R^{25}$ en donde n es 0, 1, o 2; y R^{25} es OH, OMe, F, CN, CF_3 , $SOCH_3$ o SO_2CH_3 , $-NR_{30}COR_{31}$, $-NR_{30}COOR_{31}$, $-NR_{30}SO_2R_{31}$, $-C(O)NR_{30}R_{31}$, o tiene la fórmula



En donde R^{33} es hidrógeno, alquilo, o alquilo sustituido.

42. Los compuestos de acuerdo a la reivindicación 39 en donde R^{15} es etilo, metoxietilo, CH_2CH_2F , o CH_2CH_2CN ; R^{17} es bromo o cloro; R^{18} es metoxi o hidrógeno; y R^{19} es hidrógeno.

43. Un compuesto tiene la fórmula



En donde

R^{15} es hidrógeno, alquilo, arilo, o alquilo- R^{25} ;

R^{25} es hidrógeno, hidroxilo, tiol, alqueno, alcoxi, tioalcoxi, amino, halo, ciano, sulfoxi, sulfonilo,

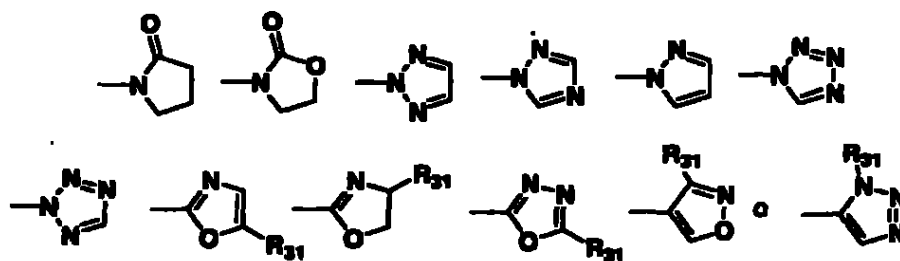
$-NR^{30}COOR^{31}$, $-NR^{30}C(O)^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$,

heteroarilo o heterocicloalquilo;

R^{17} , R^{18} y R^{19} son, independientemente, hidrógeno, halógeno, o alcoxi; o R^{18} y R^{19} juntos forman un grupo heterocicloalquilo o heteroarilo; y R^{30} y R^{31} son, independientemente, hidrogeno, alquilo, cicloalquilo o alquilo- R^{25} .



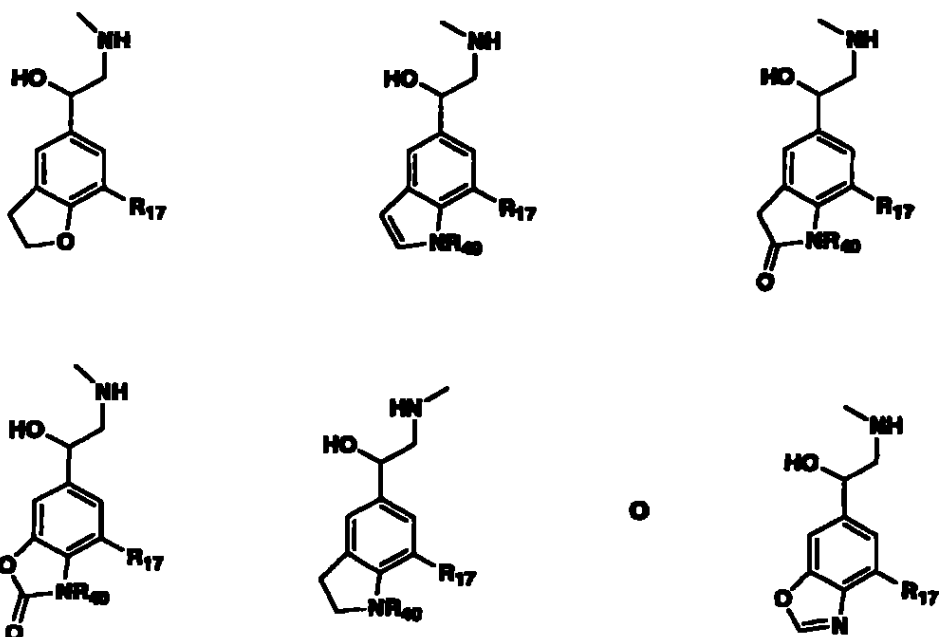
44. El compuesto acuerdo a la reivindicación 43 en donde R^{15} es $-(CH_2)_nCH_2-R^{25}$ en donde n es 0, 1, 2 o 3 y R^{25} es OH, OMe, F, CN, CF_3 , $SOCH_3$ o SO_2CH_3 , $-NR^{30}C(O)R^{31}$, $-NR^{30}COOR^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{31}R^{32}$, o tiene la fórmula:



en donde R^{33} es hidrógeno, alquilo, o alquilo sustituido.

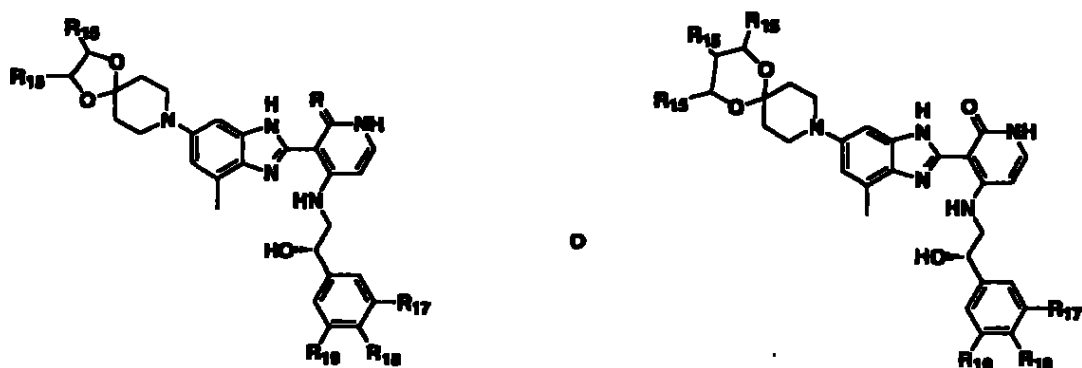
45. El compuesto de acuerdo a la reivindicación 43 en donde R^{15} es metilo, etilo, CH_2F , metoxietilo, CH_2CH_2F , o $CH_2CH_2CH_2SOCH_3$, R^{17} es bromo; R^{18} es hidrógeno, metoxi, o fluoro; y R^{19} es H.

46. El compuesto de acuerdo a la reivindicación 45 incorpora la cadena lateral



En donde R^{40} es hidrógeno o alquilo, y R^{17} es hidrógeno o halo.

47. Un compuesto tiene la formula



En donde cada R^{15} es independientemente hidrógeno, alquilo, arilo, o -alquil- R^{25} ;

8/8
519

R^{25} es hidrógeno, hidroxilo, tiol, alqueno, tioalcoxi, amina, halo, ciano, sulfoxi, sulfonil, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroarilo o heterocicloalquilo;

R^{17} , R^{18} y R^{19} son, independientes, hidrógeno, halógeno, o alcoxi; o R^{18} y R^{19} juntos forman un grupo heterociclo o heteroarilo; y

R^{30} y R^{31} son, independientes, hidrógeno, alquilo, cicloalquilo o alquil- R^{25} .

El compuesto de acuerdo a la reivindicación 1 seleccionado a partir del grupo que consiste de:

Un compuesto de acuerdo a la reivindicación 1 que tiene la fórmula:

(S)-4-(2-Hidroxi-1-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-Hidroxi-2-(3-iodo-fenilo)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(2-Cloro-fenilo)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benziminazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(3-Cloro-fenilo)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benziminazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(4-Cloro-fenilo)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benziminazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(2-Bromo-fenilo)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(3-Bromo-fenilo)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

694
521

(±)-4-(1-Hidroximetil-2-pentafluorfenil-etilamino)-
3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-
piridin-2-ona;

(S)-4-(1-Hidroximetil-2-piridin-4-il-etilamino)-3-
(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-
piridin-2-ona;

(S)-4-[1-Hidroximetil-2-(2-naftalenilo)-etilamino)]-
3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-
piridin-2-ona;

3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-4-
(piridin-2-ilmetoxi)-1H-piridin-2-ona;

(±)-4-[2-(3-Bromo-fenilo)-2-fluoro-etilamino]-3-(6-
imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-
ona;

(S)-2-[4-(1-Hidroximetil-2-fenil-etilamino)-2-oxo-
1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-
carbonitrilo;

527

(±)-2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benziminazol-5-carbonitrilo;

(S)-2-{4-[2-(3-Cloro-fenilo)-1-hidroximetil-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benziminazol-5-carbonitrilo;

(±)-2-{4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benziminazol-5-carbonitrilo;

(±)-2-{4-[2-(3-Fluoro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benziminazol-5-carbonitrilo;

(±)-2-{4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benziminazol-5-carbonitrilo;

(S)-2-[4-(2-Hidroxi-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benziminazol-5-carbonitrilo;

523

(±)-3-(1H-Benzimidazol-2-il)-4-[2-(3-bromo-fenilo)-
2-hidroxi-etilamino]-1H-piridin-2-ona;

(S)-3-(1H-Benzimidazol-2-il)-4-(1-hidroximetil-2-
fenil-etilamino)-1H-piridin-2-ona;

(±)-3-(1H-Benzimidazol-2-il)-4-[2-(3-bromo-4-metoxi-
fenilo)-2-hidroxi-etilamino]-1H-piridin-2-ona;

Ácido (S)-4-{2-[4-(1-Hidroximetil-2-fenil-etilamino)-
2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-
5-il}-piperacina-1-carboxílico isopropilamida;

Ácido (S)-4-{2-[4-(1-Hidroximetil-2-fenil-etilamino)-
2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-
5-il}-piperacina-1-carboxílico etilamida;

(S)-4-(1-Hidroximetil-2-fenil-etilamino)-3-{4-metil-
6-[4-(1-fenil-metanoil)-piperazin-1-il]-1H-benzimidazol-
2-il}-1H-piridin-2-ona;

7
524

(S)-4-(1-Hidroximetil-2-fenil-etilamino)-3-[6-(4-isopropil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-3-[6-(4-Benzil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-(1-Hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona;

(±)-3-[6-(4-Acetilo-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-[2-(3-cloro-fenilo)-2-Hidroxi-etilamino)-1H-piridin-2-ona;

(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[6-(4-isopropil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-6-(1-Hidroximetil-2-fenil-etilamino)-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-3H-piridin-4-ona;

(S)-2-[6-Cloro-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-pirimidin-4-ilamino]-3-fenil-propan-1-il;

525

(S)-4-(2-Hidroxi-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(R)-4-(2-Hidroxi-2-fenil-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(1S,2R)-4-(1-Hidroxi-indan-2-ilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-Hidroxi-2-(3-hidroxi-fenil)-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(S)-4-(2-Hidroxi-2-piridin-2-il-etilamino)-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-N-(3-{1-Hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etilo}-fenil)-metanesulfonamida;

(±)-4-[2-(3-Fluoro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

526

(±)-4-[2-(3-Cloro-4-fluoro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(3-Fluoro-fenil)-1-hidroximetil-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

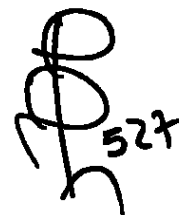
(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(R)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;



(±)-4-[2-(3-Cloro-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

Ácido (±)-(2-Cloro-4-{1-hidroxi-2-[3-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-2-oxo-1,2-dihidro-piridin-4-ilamino]-etil]-fenil)-carbónico metil éster;

(s)-4-(1-Hidroximetil-2-fenil-etilamino)-3-[4-metil-6-(4-metil-piperazin-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(s)-4-(1-Hidroximetil-2-fenil-etilamino)-3-[4-metil-6-(4-n-butil-piperazin-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(s)-3-{6-[4-2-Hidroxi-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-4-(1-hidroximetil-2-fenil-etilamino)-1H-piridin-2-ona;

Ácido (s)-4-{2-[4-(1-Hidroximetil-2-fenil-etilamino)-2-oxo-1,2-dihidro-piridin-3-il]-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico amida;

(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[6-(4-etil-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[6-[4-(2-hidroxi-etil)piperazin-1-il]-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-;

(±)-4-[2-(3-Bromo-4-metoxi-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-3-[6-[4-(2-hidroxi-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

27
15
329

(±)-4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-4-[2-(3-Bromo-fenil)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(±)-3-[6-(4-Acetilo-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-[2-(3-bromo-fenil)-2-hidroxi-etilamino]-1H-piridin-2-ona;

(s)-4-(1-Hidroxi-metil-2-fenil-etilamino)-3-[4-metil-6-(2-morfolin-4-il-etilamino)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(±)-6-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-5-(6-imidazol-1-il-4-metil-1H-benzimidazol-2-il)-3H-pirimidin-4-ona;

(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-[6-(1-hidroxi-1-metil-etil)-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(±)-3-(6-Aminometil-4-metil-1H-benzimidazol-2-il)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-1H-piridin-2-ona;



(±)-4-[2-(3-Cloro-fenil)-2-hidroxi-etilamino]-3-(6-hidroximetil-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

(s)-4-(1-Benzil-2-Hidroxi-etilamino)-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona; y

(s)-4-(1-Benzil-2-Hidroxi-etilamino)-3-(4-metil-6-piperidin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

49. El compuesto de acuerdo a la reivindicación 1 seleccionado a partir del grupo que consiste de:

(s)-4-(1-Benzil-2-Hidroxi-etilamino)-3-(4-metil-6-piperidin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-4-metilsulfanil-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-4-fluoro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-piperazin-1-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

531

3-[4-(2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-il]propionitrilo;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-metanosulfonil-etilo)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

3-[4-(2-{4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-3H-benzimidazol-5-il)-7-metil-piperazin-1-il]propionitrilo;

Ácido 4-(2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico 2-fluoro-etil éster;

Ácido 4-(2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico 2-metoxi-etil éster;

Ácido 4-(2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico tert-butil éster;

Ácido 4-(2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico prop-2-inil éster;

Ácido 4-(2-{4-[2-(3-bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico Pert butil éster;

Ácido (s)-4-(2-{4-[2-(3-bromo-4-metoxi-fenilo)-2-Hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carboxílico etil éster;

4-[2-(3-Cloro-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(3-fluoro-propil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-fluoro-etil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-4-fluoro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(3-fluoro-propil)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

533 376

4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-
3-{6-[4-(3-fluoro-propil)-piperazin-1-il]-4-metil-1H-
benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{4-
metil-6-[4-(3,3,3-trifluoro-propil)-piperazin-1-il]-1H-
benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-
(3-fluoro-propil)-piperazin-1-il]-4-metil-1H-
benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{4-
metil-6-[4-(3,4,4-trifluoro-but-3-enil)-piperazin-1-il]-
1H-benzimidazol-2-il}-1H piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-
(3-fluoro-2-hidroxi-propil)-piperazin-1-il]-4-metil-1H-
benzimidazol-2-il}-1H piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-
(2-hidroxi-2-metil-propil)-piperazin-1-il]-4-metil-1H-
benzimidazol-2-il}-1H-piridin-2-ona;

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-
[4-(2-hidroxi-etilo)-piperazin-1-il]-4-metil-1H-
benzimidazol-2-il}-1H-piridin-2-ona;

(S)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-hidroxi-etilo)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

[4-(2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-il]-acetonitrilo;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(4-fluoro-butiril)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2,2-difluoro-acetilo)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-metanosulfonil-acetilo)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

3-[6-(4-Acetilo-piperazin-1-il)-4-metil-1H-benzimidazol-2-il]-4-[2-(3-cloro-fenilo)-2-hidroxi-etilamina]-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-[4-[2-(1-oxo-114-tiomorfolin-4-il)-acetilo]-piperazin-1-il]-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-[4-[2-(1,1-dioxo-116-tiomorfolin-4-il)-acetilo]-piperazin-1-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-[4-(2-tiomorfolin-4-il-acetilo)-piperazin-1-il]-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-[4-(2-metanosulfonil-acetilo)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(6-[4-(2-metoxi-acetilo)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-[4-(2-metisulfonil-acetilo)-piperazin-1-il]-1H-benzimidazol-2-il)-1H-piridin-2-ona;

3-(6-[4-(2-Cloro-acetilo)-piperazin-1-il]-4-metil-1H-benzimidazol-2-il)-4-[2-(3-cloro-fenilo)-2-hidroxi-etilamina]-1H-piridin-2-ona;

(S)-4-(2-{4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carbaldehido;

(S)-4-(2-{4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-2-oxo-1,2-dihidro-piridin-3-il}-7-metil-3H-benzimidazol-5-il)-piperazin-1-carbaldehido;

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-4-fluoro-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il-1H-benzimidazol-2-il)-1H-piridin-2-ona;

537 

4-[2-(7-Bromo-2,3-dihidro-benzofuran-5-il)-2-hidroxi-etilamino]-3-(4-metil-6-morfolin-4-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-(S)-hidroxi-etilamino]-3-(4-metil-6-[2(S), 6(R)-dimetil-morfolin-4-il]-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Bromo-4-metoxi-fenilo)-2-(S)-hidroxi-etilamino]-3-[4-metil-6-[2(S), 6(R)-dimetil-morfolin-4-il]-1H-benzimidazol-2-il]-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-cloro-fenilo)-(S)-2-hidroxi-etelamino]-3-{6-[(S)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Bromo-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-bromo-4-metoxi-fenilo)-(S)-2-hidroxi-etelamino]-3-{6-[(S)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

538 

4-[2-(3-Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(7-Bromo-2,3-dihidro-benzofuran-4-il-4)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(7-Bromo-2,3-dihidro-benzofuran-4-il)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-fluorometil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-hidroxi-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-Cloro-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-hidroxi-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Bromo-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-hidroxi-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-Bromo-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-hidroxi-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-hidroxi-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-hidroxi-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-Cloro-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Bromo-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-Bromo-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(R)-2-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona y 4-[2-(3-Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-{6-[(S)-2-metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-(S)-2-hidroxi-etilamino]-3-(6-
 [(R)-2-metoximetil-morfolin-4-il]-4-metil-1H-
 benzimidazol-2-il)-1H-piridin-2-ona y 4-[2-(3-Cloro-
 fenilo)-(S)-2-hidroxi-etilamino]-3-(6-[(S)-2-metoxi-
 metil-morfolin-4-il]-4-metil-1H-benzimidazol-2-il)-1H-
 piridin-2-ona;

4-[2-(3-Bromo-4-metoxi-fenilo)-(S)-2-hidroxi-
 etilamino]-3-(6-[(R)-2-metoximetil-morfolin-4-il]-4-
 metil-1H-benzimidazol-2-il)-1H-piridin-2-ona y 4-[2-(3-
 Bromo-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-(6-
 [(S)-2-metoxi-metil-morfolin-4-il]-4-metil-1H-
 benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-
 etilamino]-3-(6-[(R)-2-metoximetil-morfolin-4-il]-4-
 metil-1H-benzimidazol-2-il)-1H-piridin-2-ona y 4-[2-(3-
 Cloro-4-metoxi-fenilo)-(S)-2-hidroxi-etilamino]-3-(6-
 [(S)-2-metoxi-metil-morfolin-4-il]-4-metil-1H-
 benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2(S)-hidroxi-etilamino]-3-[4-
 metil-6-(4-metil-piperadin-1-il)-1H-benzimidazol-2-il)-
 1H-piridin-2-ona;

541

4-[2-(3-Bromo-4-metoxi-fenilo)-2(S)-hidroxi-etilamino]-3-[-4-metil-6-(4-metil-piperadin-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(acetamida)-piperadin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-hidroxiacetamida)-piperidin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-fluoroacetamida)-piperidin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridina-2-ona;

4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(acetamida)-piperadin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Bromo-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2hidroxiacetamida)-piperadin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-fluoroacetamida)-piperidin-1-il]-4-metil-1H-benzimidazol-2-il}-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-metoxietoxicarbamoilo)-piperidin-1-il]-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-metoxietoxicarbamoilo)-piperidin-1-il]-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-{6-[4-(2-fluoroetoxicarbamoilo)-piperidin-1-il]-4-metil-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(2-morfolin-4-il-etoxi)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(2-morfolin-4-il-etoxi)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(2-morfolin-etoxi)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

6
11
543

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(2-hidroxi-etoxi)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-4-[2-(3-Bromo-4-metoxi-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(2-morfolin-4-il-propoxi)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(2-morfolin-4-il-propoxi)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

(S)-3-(4-Bromo-6-morfoin-4-ilmetil-1H-benzimidazol-2-il)-4-[2-(3-clomo-fenilo)-2-hidroxi-etilamino]-1H-piridin-2-ona;

(S)-3-[4-Bromo-6-(4-metil-piperazin-1-ilmeil-1H-benzimidazol-2-il)-4-[2-(3-clomo-fenilo)-2-hidroxi-etilamino]-1H-piridin-2-ona;

(S)-4-[2-(3-Cloro-fenilo)-2-hidroxi-etilamino]-3-[4-metil-6-(4-etil-6-(4-metil-piperazin-1-ilmetil)-1H-benzimidazol-2-il)-1H-piridin-2-ona;

4-[2-(3-Cloro-fenilo)-2(S)-hidroxi-etilamino]-3-[4-metil-6-(1,4,5,6-tetrahidropirimidina-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

4-[2-(4-metoxi-3-Cloro-fenilo)-2(S)-hidroxi-etilamino]-3-[4-metil-6-(1,4,5,6-tetrahidropirimidina-1-il)-1H-benzimidazol-2-il]-1H-piridin-2-ona;

50. Una composición farmacéutica comprende un compuesto de acuerdo a la reivindicación 1 y un portador aceptable farmacéuticamente.

51. La composición farmacéutica de acuerdo a la reivindicación 50 comprende además al menos un agente anti-cancerígeno formulado como una dosis fija.

52. La composición farmacéutica de acuerdo a la reivindicación 51 en donde dicho agente anti-cancerígeno se selecciona a partir del grupo que consiste de: tamoxifeno, toremifeno, raloxifeno, droloxifeno, yodoxifeno, acetato de megestrol, anastrozol, letrazol, borazol, exemestano, flutamida, nilutamida, bicalutamida, acetato de ciproterona, acetato de goserelina, luprolida, finasterida, herceptina, metotrexato, 5-fluorouracilo, arabinosida, citosina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina-C, dactinomicina, mitramicina, cisplatina, carboplatina, melfalan, clorambucil, busulfan, ciclofosfamida, ifosfamida, nitrosoureas, tiotefan, vincristina, taxol, taxotere,

etoposida, teniposida, amsacrina, irinotecan, topotecan, una epotilona, Iressa, OSI-774, inhibidores de angiogénesis, inhibidores de EGF, inhibidores de VEGF, inhibidores de CDK, inhibidores de Her1 y Her2 y anticuerpos monoclonales.

53. Un método de tratar una condición asociada con al menos una encima de tirocina cinasa comprende administrar a una especie de mamífero en necesidad de tal tratamiento una cantidad efectivo de un compuesto de acuerdo a la reivindicación 1.

54. El método de acuerdo a la reivindicación 53 en donde dicha enzima de tirocina cinasa es Abl, CDK's, EGF, EMT, FGF, FAK, Flk-1/KDR, HER-2, IGF-1R, IR, LCK, MET, PDGF, Src, o VEGF.

55. El método de acuerdo a la reivindicación 53 comprende además administrar a dicha especie de mamífero al menos otro agente anti-cancerígeno en combinación con dicha compuesto.

56. El método de acuerdo a la reivindicación 53 en donde la condición es cáncer.

57. Un método para tratar cáncer comprende administrar a una especie de mamífero en necesidad de tal

675
546

tratamiento una cantidad efectiva terapéuticamente de la composición de la reivindicación 50 o 51.

58. Un método para tratar enfermedades proliferativas comprende administrar a una especie en necesidad de tal tratamiento una cantidad efectiva terapéuticamente de la composición de la reivindicación 50 o 51.

547

RESUMEN

La presente invención suministra compuestos de fórmula (de fórmula 1) y sales farmacéuticamente aceptables de estos. Los compuestos de la fórmula I inhiben las enzimas de la tirosina cinasa haciéndolas de esta manera útiles como agentes anticancerosos. Los compuestos de fórmula I también son útiles para el tratamiento de otras enfermedades que pueden ser tratadas al inhibir las enzimas de la tirosina cinasa.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/09402

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 401/14; A61K 31/4184

US CL : 544/131, 364; 546/16, 193; 514/235.5, 253.09, 278, 318

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)

U.S. : 544/131, 364; 546/16, 193; 514/235.5, 253.09, 278, 318

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 practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHIMIRRI et al. Synthesis And Structural Features of New Cyclofunctionalized Benzimidazoles. Heterocycles. 2000, Vol. 53, No. 3, pages 613-620, especially page 615, compound 3h.	1
X	NAWWAR et al. 'Some reaction of 2-(cyanomethyl)benzothiazole versus the corresponding benzimidazole derivative.' Chem. abstr. no. 164052r, Vol. 120, No. 13, 28 March 1994 (Columbus, OH, USA), page 1172, column 1.	1
X	PEDNEKAR et al. 'Synthesis of benzimidazole-substituted pyridones azo disperse dyes.' Chem. abstr. no. 182731b, Vol. 96, No. 22, 31 May 1982 (Columbus, OH, USA), page 87, column 2.	1

☐ Further documents are listed in the continuation of Box C.☐ See patent family 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 application or patent 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

"A"

document member of the same patent family

Date of the actual completion of the international search

16 July 2002 (16.07.2002)

Date of mailing of the international search report

27 AUG 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

Box PCT

Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Deepak Rao

Felicia D. Roberts for

Telephone No. (703) 308-1235



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20531
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/279,327	03/28/2001		150	LD0227 (PSP)			

CONFIRMATION N . 1375

FILING RECEIPT



OC000000008281087

23914
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

Date Mailed: 07/11/2001

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Mark D. Wittman, Wallingford, CT; ✓
Neelakantan Balasubramanian, Madison, CT; ✓
Karen Mary Bedingfield, West Hartford, CT; ✓
Pelying Liu, Madison, CT; ✓
Xiaopeng Sang, Glastonbury, CT; ✓
James G. Tarrant, Hamden, CT; ✓
Upender Velaparthi, North Haven, CT; ✓
Kurt Zimmermann, Durham, CT; ✓

RECEIVED	
U.S. Patent Law	
JUL 16 2001	
Docketed item	_____
Due Date	_____
Attorney	<u>KEN</u>

If Required, Foreign Filing License Granted 07/10/2001 ✓

Projected Publication Date: N/A

Non-Publication Request: No

Early Publication Request: No

Title

Novel tyrosine kinase inhibitors ✓

7/17/01
C/MO

550

Data entry by : SAYSON, KLEITON

Team : OIPE

Date: 07/11/2001

|||||

**LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15**

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PLEASE NOTE the following information about the Filing Receipt:

- The articles such as "a," "an" and "the" are not included as the first words in the title of an application. They are considered to be unnecessary to the understanding of the title.
- The words "new," "improved," "improvements in" or "relating to" are not included as first words in the title of an application because a patent application, by nature, is a new idea or improvement.
- The title may be truncated if it consists of more than 500 characters (letters and spaces combined).
- The docket number allows a maximum of 25 characters.
- If your application was submitted under 37 CFR 1.10, your filing date should be the "date in" found on the Express Mail label. If there is a discrepancy, you should submit a request for a corrected Filing Receipt along with a copy of the Express Mail label showing the "date in."
- The title is recorded in sentence case.

Any corrections that may need to be done to your Filing Receipt should be directed to:

Assistant Commissioner for Patents
Office of Initial Patent Examination
Customer Service Center
Washington, DC 20231



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20530
www.uspto.gov

LD 0227 NP

APPLICATION NUMBER	FILING DATE	GROSS AMT	FILED RECD	ATTY DOKT NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/105,599	03/26/2002	1,000.00	03/26/2002	00000000		58	7

AUG 05 2002

CONFIRMATION NO. 8843

Stephen B. Davis
Bristol-Myers Squibb Company
Patent Department
P. O. Box 4000
Princeton, NJ 08543-4000

Docketed Items

UPDATED FILING RECEIPT

Due Date

Abstract

Data Mailed: 07/30/2002

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-748-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Mark D. Wittman, Wallingford, CT; ✓
Neelakantan Balasubramanian, Madison, CT; ✓
Upender Veluparthi, North Haven, CT; ✓
Kurt Zimmermann, Durham, CT; ✓
Mark G. Saulnier, Higganum, CT; ✓
Pelyng Lhu, Madison, CT; ✓
Xiaopeng Sang, Glastonbury, CT; ✓
David B. Frennesson, Naugatuck, CT; ✓
Karen M. Stoffan, Hartford, CT; ✓
James G. Tarrant, Hamden, CT; ✓

✓ correct.
~~XXXXXXXXXX~~

Domestic Priority data as claimed by applicant

THIS APPLN CLAIMS BENEFIT OF 60/279,327 03/28/2001

Foreign Applications

If Required, Foreign Filing License Granted 05/07/2002

Projected Publication Date: 11/07/2002

Non-Publication Request: No

Early Publication Request: No

File
553

Amendment Under Article 34

Patent Application No. PCT/US02/09402

Docket No. LD0227 PCT

Express mail mailing label number EV 322166685 US

Date of Deposit August 20, 2003

I hereby certify that this paper or fee is being deposited with the United States
Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10
on the date indicated above and is addressed to: Mail Stop PCT,
Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Debra A. Wojcik

(Typed or printed name of person mailing paper or fee)

Debra A. Wojcik

(Signature of person mailing paper or fee)

EV322166685US

554 *27*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

International Application No.: PCT/US02/09402
International Filing Date: 26 March 2002
Priority Date: 28 March 2001
Applicant: Bristol-Myers Squibb Company

For: NOVEL TYROSINE KINASE INHIBITORS

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT PURSUANT TO PCT ARTICLE 34
IN THE INTERNATIONAL APPLICATION

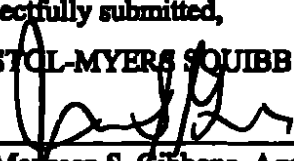
SIR:

This is a timely response to the Written Opinion mailed on July 24, 2003 in the above-referenced application. Claim 1 in the subject application has been amended as shown in the attached substitute sheets to more clearly set forth the substituents at R⁶ and R⁸. The compounds disclosed in the cited references, Nawwar et al. (RN 153259-12-2 and RN 153259-13-3); Pednekar (RN 81608-02-8 and RN 81608-03-9); Chimmiri (RN 104152-74-1) are not within the scope of the claims as amended. Thus, Applicants herewith submit replacement pages 221, 221-1, and 222. Applicants respectfully submit that no new matter is hereby being introduced into the application.

No fee is believed to be due in conjunction with this submission. However, should any fee be due, kindly charge such fee to Deposit Account No. 19-3880.

Respectfully submitted,

BRISTOL-MYERS SQUIBB COMPANY

By: 
Maureen S. Gibbons, Agent for Applicant
Reg. No. 44,121
P.O. Box 4000
Princeton, New Jersey 08543-4000
(609) 252-3453

Date: August 20, 2003

Express Mail trailing label number EV 322166685 US

Date of Deposit August 20, 2003

I hereby certify that this paper correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Mail Stop PCT, P.O. Box 1450, Alexandria, VA 22313-1450.

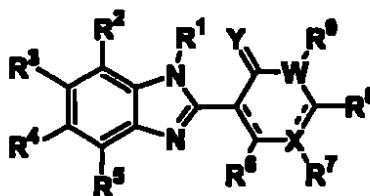
Debra A. Wojcik

(Typed or printed name of person mailing paper or fee)


(Signature of person mailing paper or fee)

What is claimed is:

1. A compound according to formula I



I

its enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs and solvates thereof;

wherein

X is selected from the group consisting of N, C, C₁-C₃ alkyl, C₁-C₃ alkyl substituted with one or more R⁷, and a direct bond;

Y is selected from the group consisting of O and S;

W is selected from the group consisting of N, C, O, and S; provided that if W is O or S, R⁹ is absent;

R¹, R², R³, R⁴, R⁵, R⁷, R⁸, R⁹ are each independently selected from the group consisting of H, C₁₋₆ alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, OR⁶⁰, NO₂, OH, SR⁶⁰, NR⁶⁰R⁶¹, CN, CO₂R⁶⁰, CONR⁶⁰R⁶¹, OCONR⁶⁰R⁶¹, NR⁶²CONR⁶⁰R⁶¹, NR⁶⁰SO₂R⁶¹, SO₂NR⁶⁰R⁶¹, C(NR⁶²)NR⁶⁰R⁶¹, aryl, heteroaryl, (CH₂)_nOR⁶⁰, (CH₂)_nNR⁶⁰R⁶¹, (CH₂)_nSR⁶⁰, (CH₂)_n aryl, (CH₂)_n heteroaryl, (CH₂)_n heterocycloalkyl, NH-Z-aryl, and NH-Z-heteroaryl;

wherein n is 1 to 3;

R⁶ is H, C₁₋₆ alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, OR⁶⁰, NO₂, OH, SR⁶⁰, NR⁶⁰R⁶¹, CN, CO₂R⁶⁰, CONR⁶⁰R⁶¹, OCONR⁶⁰R⁶¹, NR⁶²CONR⁶⁰R⁶¹, NR⁶⁰SO₂R⁶¹, SO₂NR⁶⁰R⁶¹, C(NR⁶²)NR⁶⁰R⁶¹, (CH₂)_nOR⁶⁰, (CH₂)_nNR⁶⁰R⁶¹, (CH₂)_nSR⁶⁰, (CH₂)_n aryl, (CH₂)_n heteroaryl, (CH₂)_n heterocycloalkyl, NH-Z-aryl, and NH-Z-heteroaryl provided that R⁶ is not H if Y is S; and

[Handwritten signature]

R^6 is H, C_{1-6} alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, NO_2 , OH, SR^{60} , $NR^{60}R^{61}$, CN, CO_2R^{60} , $CONR^{60}R^{61}$, $OCONR^{60}R^{61}$, $NR^{62}CONR^{60}R^{61}$, $NR^{60}SO_2R^{61}$, $SO_2NR^{60}R^{61}$, $C(NR^{62})NR^{60}R^{61}$, $(CH_2)_nOR^{60}$, $(CH_2)_nNR^{60}R^{61}$, $(CH_2)_nSR^{60}$, $(CH_2)_n$ aryl, $(CH_2)_n$ heteroaryl, , $(CH_2)_n$ heterocycloalkyl, NH-Z-aryl, and NH-Z-heteroaryl;

Z is selected from the group consisting of $C_1 - C_4$ alkyl, alkenyl, and alkynyl chain; Z having one or more hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, $NR^{60}SO_2R^{61}$ groups; Z optionally incorporating one or more groups selected from the group consisting of CO, CNOH, $CNOR^{60}$, $CNNR^{60}$, $CNNCOR^{60}$ and $CNNR^{60}SO_2R^{61}$; and

R^{60} , and R^{61} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, heteroaryl, heteroarylalkyl, and alkyl- R^{25} wherein

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and R^{30} and R^{31} are, independently, hydrogen, alkyl, cycloalkyl, or alkyl- R^{25} .

557

2. The compound according to claim 1 wherein
R¹, R⁷, R⁸ and R⁹ are H;
R² and R⁴ are H or F;
Y is O;
5 X is selected from the group consisting of N and CH;
W is N;
R⁵ is selected from the group consisting of H, methyl, ethyl, isopropyl,
secondary butyl, cyclopropyl, F, and CF₃;
R⁶ is selected from the group consisting of H, 2-aminomethylpyridine,
10 NHCH₂CH(OH)Ph, NHCH₂CH(OH)(3-Cl-Ph), NHCH₂CH(OH)(3-Br-Ph),
NHCH₂CH(OH)(3-Br-4-OMe-Ph), NHCH(CH₂OH)CH₂Ph, NHCH₂CH(OH)aryl,
and NHCH(CH₂OH)CH₂aryl; and
R³ is selected from the group consisting of OR⁶⁰, C(NH)NHR⁶⁰, C(O)NHR⁶⁰
imidazole, imidazoline, tetrahydropyrimidine, piperazine, morpholine,
15 homomorpholine, piperidine, pyrrolidine, homopiperazine and amino; wherein
R⁶⁰ is selected from the group consisting of H, alkyl, cycloalkyl,
heterocycloalkyl, and alkyl-R²⁵ wherein R²⁵ is hydrogen, alkenyl, hydroxy, thiol,
thioalkoxy, alkoxy, thioalkoxy, halo, cyano, sulfoxy, sulfonyl, -NR³⁰COOR³¹, -
NR³⁰C(O)R³¹, -NR³⁰SO₂R³¹, -C(O)NR³⁰R³¹, or a heteroaryl or heterocycloalkyl; and
20 R₃₀ and R₃₁ are, independently, hydrogen, alkyl, cycloalkyl, or alkyl-R²⁵.
3. The compound according to claim 2 wherein R³ is -OR⁶⁰ and R⁶⁰ is alkyl, or -
alkyl-R²⁵, wherein



EV 32216665 US

Mailing Label
Label 7-17 June 2002

UNITED STATES POSTAL SERVICE

Post Office To Addressee

DEFINITIONS (POSTAL USE ONLY)

PO ZIP Code	Day of Delivery ☐ Next ☐ Second ☐ Third	Flat Rate Envelope
Date In Mo. Day Year	☐ Next ☐ PM	Postage
Time ☐ AM ☐ PM	☐ Next Day ☐ Not Day	Postage Receipt Fee
Weight	Int'l Alpha Country Code	ODD Fee
Int'l Alpha Country Code	Int'l Alpha Country Code	Insurance Fee
Signature ☐ Signature ☐ No Signature	Acceptance Clerk Initials	Total Postage
		Fees

DEFINITIONS (POSTAL USE ONLY)

Delivery Attempt	Time ☐ AM ☐ PM	Employee Signature
Delivery Attempt	Time ☐ AM ☐ PM	Employee Signature
Delivery Date	Time ☐ AM ☐ PM	Employee Signature
Delivery Date	Time ☐ AM ☐ PM	Employee Signature

Express Mail Certificate No. **X085205**

FROM: (PLEASE PRINT) FROM: _____
STEPHEN DAVIS
BRISTOL-MYERS SQUIBB CO
PO BOX 4000
PRINCETON NJ 08543-4000

TO: (PLEASE PRINT) FROM: _____
MAIL STOP PCT
COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA VA 22313-1450

LD 0227 PCT MSG

Act 34 Amendment

FOR PICKUP OR TRACKING CALL 1-800-222-1811 www.usps.com



358

559 *zh*

Case No.: LD0227 PCT
Int'l Application No.: PCT/US02/09402
Mailing Date: 8-20-03

Express Mail No.: EV 322 1616085

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing:

☐ Appln. Filing Papers

☐ Transmittal Fee:

☐ Search Fee:

☐ Basic Fee:

☐ Designation Fee:

☐ Priority Document Fee:

☒ Amendment under Article 34

PATENT COOPERATION TREATY

RECEIVED

RMS PATENT LAW

2/18 JUL 28 2003

560

Docketed Item OA

Due Date 8/24/03

Attorney (MP) 8/24/03

WRITTEN OPINION

(PCT Rule 66)

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
MAUREEN GIBBONS
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

Date of Mailing
(day/month/year) 24 JUL 2003

Applicant's or agent's file reference

LD227

REPLY DUE

within 1 month/days from
the above date of mailing

International application No.

PCT/US02/09402

International filing date (day/month/year)

26 March 2002 (26.03.2002)

Priority date (day/month/year)

28 March 2001 (28.03.2001)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07D 401/14; A61K 31/4184 and US Cl.: 544/131, 364; 546/16, 193; 514/235.5, 253.08, 278, 318

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(i) 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

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 28 July 2003 (28.07.2003).

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

Debra D. Roberts for

Telephone No. (703) 308-1235

Form PCT/IPEA/408 (cover sheet)(July 1998)

I. Basis of the opinion

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
pages 1-220, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☒ the claims:
pages 221-247, 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 Rule 23.1(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 written opinion was drawn 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 opinion has been drawn 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 opinion as "originally filed."

WRITTEN OPINION

International application No.
PCT/US02/09402

562

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 2-58	YES
	Claims 1	NO
Inventive Step (IS)	Claims 2-58	YES
	Claims 1	NO
Industrial Applicability (IA)	Claims 1-58	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by NAWWAR et al. The instantly claimed compounds read on the compounds disclosed in the reference, see the compounds RN 153259-12-2 and RN 153259-13-3.

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by PEDNEKAR et al. The instantly claimed compounds read on the compounds disclosed in the reference, see the compounds RN 81608-02-8 and RN 81608-03-9.

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by CHIMMIRI et al. The instantly claimed compounds read on the compound disclosed in the reference, see the compound RN 104152-74-1.

Claim 1 lacks an inventive step under PCT Article 33(3) as being obvious over PEDNEKAR et al. The instantly claimed compounds read on the reference disclosed compounds or alternatively the analogous compounds would have been obvious to one of ordinary skill in the art in view of the dyeing properties of the reference compounds.

Claims 2-58 meet the criteria of novelty and inventive step set out in PCT Article 33(2)-(3), because the prior art (e.g., CHIMMIRI et al.) does not teach or fairly suggest the instantly claimed compounds.

Claims 1-58 meet the criteria set out in PCT Article 33(4), as the claimed compounds are disclosed to be useful as therapeutic agents having anti-cancer activity and thus meet the criteria of industrial applicability because the subject matter claimed can be made or used in industry.

WRITTEN OPINION

International application No.
PCT/US02/09402

563

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

PATENT COOPERATION TREATY

564

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MAUREEN GIBBONS
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000RECEIVED
RMS PATENT LAW

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

Docketed Item

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Due Date

Attorney

Date of mailing
(day/month/year)

14 NOV 2002

Applicant's or agent's file reference

LD227

IMPORTANT NOTIFICATION

International application No.

PCT/US02/09402

International filing date (day/month/year)

28 Mar 2002

Priority date (day/month/year)

28 Mar 2001

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

23 OCT 2002

2. That date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

Assistant Commissioner for Patent, Box PCT
Washington, D.C. 20231 Attn: RO/US

Authorized officer

Catherine Williams

Facsimile No. 703-305-3230

Telephone No. 703-305-3677

Form PCT/IPEA/402 (July 1998)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
MAUREEN GIBBONS
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Notcketed item

Out Date

Date of Mailing
(day/month/year)

27 AUG 2002

Applicant's or agent's file reference

Attorney

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US02/09402

International filing date
(day/month/year)

26 March 2002 (26.03.2002)

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Commissioner for Patents
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
Deepak Rao
Telephone No. (703) 308-1235

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

566 

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MAUREEN GIBBONS
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

		Date of Mailing (day/month/year)	27 AUG 2002
Applicant's or agent's file reference LD227		FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/US02/09402		International filing date (day/month/year) 26 March 2002 (26.03.2002)	
Applicant BRISTOL-MYERS SQUIBB COMPANY			

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Deepak Rao <i>Felicia D. Roberts for</i> Telephone No. (703) 308-1235
---	--

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

567

5

Applicant's or agent's file reference LD227	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.
International application No. PCT/US02/09402	International filing date (day/month/year) 26 March 2002 (26.03.2002)	(Earliest) Priority Date (day/month/year) 28 March 2001 (28.03.2001)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written 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.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 34.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/09402

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 401/14; A61K 31/4184
US CL : 544/131, 364; 546/16, 193; 514/235.5, 253.09, 278, 318

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)
U.S. : 544/131, 364; 546/16, 193; 514/235.5, 253.09, 278, 318

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 practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHIMIRRI et al. Synthesis And Structural Features of New Cyclofunctionalized Benzimidazoles. Heterocycles. 2000, Vol. 53, No. 3, pages 613-620, especially page 615, compound 3h.	1
X	NAWWAR et al. 'Some reaction of 2-(cyanomethyl)benzothiazole versus the corresponding benzimidazole derivative.' Chem. abstr. no. 164052r, Vol. 120, No. 13, 28 March 1994 (Columbus, OH, USA), page 1172, column 1.	1
X	PEDNEKAR et al. 'Synthesis of benzimidazole-substituted pyridones and disperse dyes.' Chem. abstr. no. 182731b, Vol. 96, No. 22, 31 May 1982 (Columbus, OH, USA), page 87, column 2.	1

☐ Further documents are listed in the continuation of Box C.	☐ See patent family annex.
* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"Y" 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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family
"T" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 16 July 2002 (16.07.2002)	Date of mailing of the international search report 27 AUG 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20531 Facsimile No. (703)305-3230	Authorized officer Deepak Rao Felicia D. Roberts yfor Telephone No. (703) 308-1235

569

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

**POST OFFICE
TO ADDRESSEE**



UNITED STATES POSTAL SERVICE™

PO ZIP Code	8108	Day of Delivery	☒ 10/23/02	Post Office	☐
City	10/23/02	Time of Delivery	10:30 AM	Post Office	10:30 AM
State	UT	Post Office	10:30 AM	Post Office	10:30 AM
Post Office	10:30 AM	Post Office	10:30 AM	Post Office	10:30 AM
Post Office	10:30 AM	Post Office	10:30 AM	Post Office	10:30 AM
Post Office	10:30 AM	Post Office	10:30 AM	Post Office	10:30 AM

EL596928597US

SEE REVERSE SIDE FOR
SERVICE GUARANTEE AND LIMITS
ON INSURANCE COVERAGE

NAME OF ADDRESSEE	Stephen Davis
ADDRESS	WISCONSIN 53101-0000
CITY	MILWAUKEE
STATE	WI
ZIP CODE	53101-0000
POST OFFICE	10:30 AM
POST OFFICE	10:30 AM
POST OFFICE	10:30 AM

FOR PATENT
WASHINGTON
LC 202 1-9495
BOX 101

FOR PICKUP OR TRACKING CALL 1-800-222-1811 WWW.USPS.GOV

2412

570

Case N LD227 PCT
Application No PCT/US02/09402
Mailing Date October 23, 2002
Express Mail No EL596928597US
The patent and Trademark Office acknowledges and has stamped hereon the date of receipt of the items checked below for PCT filing

- ☐ Appln Filing Papers
- ☐ Transmittal Fee
- ☐ Search Fee
- ☐ Basic Fee UT19 Rec'd PCT/PTO 23 OCT 2002
- ☐ Designation Fee
- ☐ Priority Document Fee
- ☒ Demand

7/11/02
571

Int'l. Application No. PCT/US02/09402

Docket No. LD227

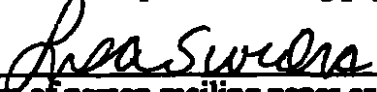
**RESPONSE TO INVITATION TO PAY PRESCRIBED FEES TOGETHER WITH LATE
PAYMENT FEE**

Express mail mailing label number EL596928597US

Date of Deposit October 23, 2002

I hereby certify that this paper or fee is being deposited with the United States
Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10
on the date indicated above and is addressed to the Assistant Commissioner for
Patents, Box PCT, Washington, D.C. 20231.

Lisa Swidra
(Typed or printed name of person mailing paper or fee)


(Signature of person mailing paper or fee)

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below.

IPRA/ US

PCT

CHAPTER II

DEMAND

572

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 IPRA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference LD227	
International application No. PCT/US02/09402	International filing date (day/month/year) (28.03.02) 28.MARCH.2002	(Earliest) Priority date (day/month/year) (28.03.01) 28.MARCH.01	
Title of invention NOVEL TYROSINE KINASE INHIBITORS			
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.) Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America		Telephone No. 609-252-3453	
		Facsimile No. 609-252-4526	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: United States of America		State (that is, country) of residence: United States of America	
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.) WITTMAN, Mark, D. 30 Fairlawn Drive Wallingford, CT 06492 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: 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.) BALASUBRAMANIAN, Neelakantan 26 Horsebarn Lane Madison, CT 06443 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

VELAPARTHI, Upender
1298 Hartford Turnpike #9J
North Haven, CT 06422
UNITED STATES OF AMERICA

State (that is, country) of nationality:
IN

State (that is, country) of residence:
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.)

ZIMMERMANN, Kurt
5 Skeetfield Point Road
Durham, CT 06422
UNITED STATES OF AMERICA

State (that is, country) of nationality:
AT

State (that is, country) of residence:
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.)

SAULNIER, Mark, G.
34 Ponsett Road
Higganum, CT 06441
UNITED STATES OF AMERICA

State (that is, country) of nationality:
US

State (that is, country) of residence:
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.)

LIU, Pelying
228 Devonshire Lane
Madison, CT 06443
UNITED STATES OF AMERICA

State (that is, country) of nationality:
CA

State (that is, country) of residence:
US

☒ Further applicants are indicated on another continuation sheet.

Continuation of Box No. II APPLICANT(S)

57.4

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.)

SANG, Xiaopeng
45 Hawthorne Mead Drive
Glastonbury, CT 06033
UNITED STATE OF AMERICA

State (that is, country) of nationality:
CNState (that is, country) of residence:
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.)

FRENNESSON, David, B.
164 Conrad Street
Naugatuck, CT 06770
UNITED STATES OF AMERICA

State (that is, country) of nationality:
USState (that is, country) of residence:
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.)

STOFFAN, Karen, M.
149 Whitney Street
Hartford, CT 06105
UNITED STATES OF AMERICA

State (that is, country) of nationality:
USState (that is, country) of residence:
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.)

TARRANT, James, G.
156 Handy Road
Hamden, CT 06518
UNITED STATES OF AMERICA

State (that is, country) of nationality:
USState (that is, country) of residence:
US☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)GIBBONS, Maureen
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Telephone No.

609-252-3453

Facsimile No.

609-252-4526

Teleprinter No.

Agent's registration No. with the Office

44,121

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the languages referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|----------|
| 1. translation of international application | : | 0 sheets |
| 2. amendments under Article 34 | : | 0 sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | 0 sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | 0 sheets |
| 5. letter | : | 0 sheets |
| 6. other (specify) | : | 0 sheets |

For International Preliminary Examining Authority use only
received not received

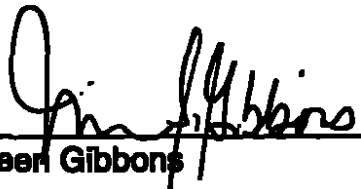
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (Certification for POA): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

 Agent Date: 10/23/02
Maureen Gibbons

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:

577

These Notes are intended to facilitate the filling in of the demand form and to give some information concerning international preliminary examination under Chapter II of the Patent Cooperation Treaty (PCT). For more detailed information, see the *PCT Applicant's Guide*, a WIPO publication, which is available, together with other PCT related documents, at WIPO's Website www.wipo.int/pct/en/index.html. The Notes are based on the requirements of the PCT, the Regulations and the Administrative Instructions under the PCT. In case of any discrepancy between these Notes and those requirements, the latter are applicable.

In the demand form and these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the Administrative Instructions, respectively.

Please use a typewriter; check-boxes may be marked by hand with dark ink (Rules 11.9(a) and (b) and 11.14).

The demand form and these Notes may be downloaded from WIPO's Website at the address given above.

IMPORTANT GENERAL INFORMATION

Who May File a Demand? (Article 31(2)(a) and Rule 54): A demand (for international preliminary examination) may only be filed by an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II of the PCT; furthermore, the international application must have been filed with a receiving Office of, or acting for, a State bound by Chapter II. Where there are two or more applicants (for the same or different elected States) at least one of them must qualify.

Where Must the Demand Be Filed? (Article 31(8)(a)): The demand must be filed with a competent International Preliminary Examining Authority (IPEA). The receiving Office with which the international application was filed will, upon request, give information about the competent IPEA (or see the *PCT Applicant's Guide*, Volume I/B, Annex C). If several IPEAs are competent, the applicant has the choice and the demand must be filed with (and the fees must be paid to) the IPEA chosen by the applicant. The IPEA chosen by the applicant may be identified, preferably by an indication of the name or two-letter code of the IPEA, at the top of the first sheet of the demand in the space provided for that purpose.

When Must the Demand Be Filed? (Article 39(1)): The demand must be filed before the expiration of 18 months from the priority date in order to extend the time limit for entering the national phase of the PCT procedure from 20 to 30 months from the priority date. *Warning:* If the demand is filed later, the national phase will not be delayed in respect of the elected States and the applicant must enter the national phase before the expiration of the time limit applicable under Article 22 (which is usually 20 months from the priority date).

In Which Language Must the Demand Be Filed? (Rule 55.1): The demand must be filed in the language in which international preliminary examination will be carried out (see Notes to Box No. IV).

What is the Language of Correspondence? (Rules 66.9 and 82.2 and Section 104): Any letter from the applicant to the IPEA must be in the same language as the international application to which it relates. However, where the international preliminary examination will be carried out on the basis of a translation (see Notes to Box No. IV), any letter from the applicant to the IPEA must be in the language of the translation. The IPEA may authorize the use of other languages for letters which do not contain or relate to amendments of the international application. Any letter from the applicant to the International Bureau must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Which Fees Must Be Paid and When? (Rules 57 and 58): Two fees are due in respect of the international preliminary examination: the preliminary examination fee and the handling fee. Both fees must be paid to the IPEA within one month from the date on which the demand is submitted. The Fee Calculation Sheet should be used for that purpose. For details concerning the payment of the fees, see the Notes to that Sheet.

BOX No. I

Applicant's or Agent's File Reference: A file reference may be indicated, if desired. It should not exceed 12 characters. Characters in excess of 12 may be disregarded (Section 109).

Identification of the International Application (Rule 53.6): The international application number must be indicated in Box No. I. Where the demand is filed at a time when the international application number has not yet been notified by the receiving Office, the name of that Office must be indicated instead of the international application number.

International Filing Date and (Earliest) Priority Date (Section 110): Dates must be indicated by the Arabic number of the day, the name of the month and the Arabic number of the year—in that order; after, below or above such indication, the date should be repeated in parentheses, using two-digit Arabic numerals for each of the number of the day, the number of the month and the last two digits of the year, in that order, and separated by periods, slants or hyphens, for example, "20 March 2001 (20.03.01)", "20 March 2001 (20/03/01)" or "20 March 2001 (20-03-01)". Where the international application claims the priority of several earlier applications, the filing date of the earliest application whose priority is claimed must be indicated as the priority date.

Title of the Invention: If a new title has been established by the International Searching Authority, that title must be indicated in Box No. I.

BOX No. II

Applicant(s) (Rule 53.4): All the applicants for the elected States must be indicated in the demand; an applicant named in the request (Form PCT/RO/101) for a State which is not elected need not be named in the demand. It should be noted that the persons named as "inventor only" in the request need not be named in the demand.

Make in Box No. II of the demand the required indications as appearing in Boxes Nos. II and III of the request. The Notes to the request apply *mutatis mutandis*. If there are two or more applicants for the States elected in the demand, give the required indications for each of them; if there are more than

three applicants, make the required indications on the "Continuation Sheet".

If different applicants are indicated in the request for different designated States, indicate in Box No. II of the demand only the applicants for the States elected in Box No. V (no indication of the States for which a person is applicant need be made, because those indications have been made in the request).

Applicant's registration number with the Office (Rule 53.4): Where the applicant is registered with the national or regional Office that is acting as International Preliminary Examining Authority, the demand may indicate the number or other indication under which the applicant is so registered.

BOX No. III

Agent or Common Representative (Rules 53.5, 90.1 and 90.2): Mark the applicable check-boxes to indicate *first* whether the person named in this Box is agent or common representative, *then* whether that person *has been appointed earlier* (i.e., during the procedure under Chapter I), or *is appointed in the demand* and any earlier appointment of another person is revoked, or *is appointed specifically for the procedure before the IPEA* (without revocation of any earlier appointment), in addition to the person(s) appointed earlier.

Where an additional person is appointed specifically for the procedure before the IPEA, all notifications issued by the IPEA will be addressed only to that additional person.

A separate power of attorney must be filed with the IPEA, the International Bureau or the receiving Office, if the person appointed at the time the demand is filed (i.e., was not appointed earlier) signs the demand on behalf of the applicant (Rule 90.4).

Agent's registration number with the Office (Rule 53.5): Where the agent is registered with the national or regional Office that is acting as International Preliminary Examining Authority, the demand may indicate the number or other indication under which the agent is so registered.

Address for Correspondence (Rule 4.4(d) and Section 108): Where an agent is appointed, any correspondence intended for the applicant will be sent to the address indicated for that agent (or for the first-mentioned agent, if more than one is appointed). Where one of two or more applicants is appointed as common representative, the address indicated for that applicant in Box No. III will be used.

Where no agent or common representative is appointed, any correspondence will be sent to the address, indicated in Box No. II, of the applicant (if only one person is named as applicant) or of the applicant who is considered to be common representative (if there are two or more persons named as applicants). However, if the applicant wishes correspondence to be sent to a different address in such a case, that address may be indicated in Box No. III instead of the designation of an agent or common representative. In this case, and only in this case, the last check-box of Box No. III must be marked (that is, the last check-box must not be marked if either of the check-boxes "agent" or "common representative" in Box No. III has been marked).

BOX No. IV

Statement Concerning Amendments (Rules 53.2(a)(v), 53.9, 62, 66.1 and 69.1): The international preliminary examination will start on the basis of the international application

as filed or, if amendments have been filed, as amended. Mark the appropriate check-box(es) to enable the IPEA to determine when and on what basis it can start international preliminary examination.

Mark the corresponding check-box(es) under No. 1 where the international preliminary examination should start on the basis of the international application as originally filed or where amendments are to be taken into account, as the case may be. Where amendments are to be taken into account, the applicant must submit *with the demand* a copy of amendments to the claims under Article 19 (Rule 53.9(a)(i)) and/or the amendments of the international application under Article 34 (Rule 53.9(c)), as the case may be. If a check-box is marked but the demand is not accompanied by the documents referred to, the start of international preliminary examination will be delayed until the IPEA receives them.

Mark check-box No. 2 if amendments of the claims under Article 19 have been filed with the International Bureau during the Chapter I procedure, but the applicant does not want these amendments to be taken into account for the purpose of international preliminary examination when the latter starts (Rule 53.9(a)(ii)).

Mark check-box No. 3 where the time limit for filing amendments of the claims under Article 19 has not expired at the time the demand is filed and the applicant wants to keep the option for the filing of such amendments open; the IPEA is thus requested to postpone the start of international preliminary examination (Rules 53.9(b) and 69.1(d)). It should be noted that the examination will start in any event after the expiration of 20 months from the priority date even where the time limit for filing amendments has not yet expired or no amendments have been received by the IPEA.

If no check-box is marked, refer to the footnote at the bottom of the Box.

Language for the Purposes of International Preliminary Examination (Rule 55.2): Where neither the language in which the international application is filed nor the language in which the international application is published is accepted by the IPEA that is to carry out the international preliminary examination, the applicant must furnish with the demand a translation of the international application into a language which is both a language accepted by that Authority and a language of publication.

Where such translation has already been furnished to the International Searching Authority for the purposes of carrying out international search and the IPEA is part of the same Office or intergovernmental organization as the International Searching Authority, the applicant need not furnish another translation. In such a case the international preliminary examination is carried out on the basis of the translation furnished for the purposes of international search.

The language for the purposes of international preliminary examination should be indicated in Box No. IV, on the dotted line, and the corresponding check-box should be marked.

Language of Amendments (Rules 55.3 and 69.9): Amendments and letters relating thereto must be in the same language as that in which the international preliminary examination is carried out, as explained in the preceding paragraphs.

Time Limit for Furnishing Translation of the International Application (Rule 55.2): Any required translation of the international application should be furnished (by the applicant) together with the demand. If it is not so furnished, the IPEA will invite the applicant to furnish it within a time limit which shall not be less than one month from the date of the invitation. That time limit may be extended by the IPEA.

BOX No. V

Election of States (Rule 53.7): Only States which are bound by Chapter II of the PCT and which have been designated in the international application (that is, States whose designations have been made under Rule 4.9(a), confirmed under Rule 4.9(c) or considered as having been made under Rule 32.2(a)(i)) can be elected. They are the "eligible States".

For the convenience and protection of applicants, Box No. V contains a statement to the effect that all eligible States are elected. It is only where the applicant does not wish to elect certain eligible States that the name(s) or two-letter code(s) of those States must be indicated after the words "wishes not to elect".

The indication in the demand of the kind of protection or treatment desired for any elected State is not required since it follows the indication made when designating that State in the international application.

BOX No. VI

Check List: It is recommended that this Box be filled in carefully in order for the IPEA to determine as soon as possible whether it is in possession of the documents on the basis of which the applicant wishes international preliminary examination to start.

Where the international application contains disclosure of one or more nucleotide and/or amino acid sequences, and a copy of the sequence listing in computer readable form complying with the standard provided for in the Administrative Instructions is required by the IPEA, the applicant may furnish the listing in computer readable form to the IPEA with the demand. If this is the case, check-box No. 5 must be marked.

BOX No. VII

Signature (Rules 53.8, 90.3(a) and 90.4(a)): The demand must be signed by the applicant or by his agent; if there are two or more applicants, the common representative may sign the demand. If the demand is not signed by (all) the persons who are applicants for the elected States (a person who is applicant only for a State which is not elected need not sign the demand), a power of attorney signed by that (all those) applicant(s) must be filed with the IPEA, with the International Bureau or with the receiving Office unless the agent has previously been appointed.

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand

580

International application No. PCT/US02/09402 Applicant's or agent's file reference LD227 Applicant Bristol-Myers Squibb Company CALCULATION OF PRESCRIBED FEES 1. Preliminary examination fee 490.00 P 2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) 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	For International Preliminary Examining Authority use only Date stamp of the IPEA								
MODE OF PAYMENT <table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs) <table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> ☒ Authorization to charge the total fees indicated above. ☒ (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. </td> <td style="width: 50%; vertical-align: top;"> IPEA/US _____ Deposit Account No.: <u>19-3880</u> Date: <u>October 23, 2002</u> Name: <u>Maureen Gibbons</u> Signature: <u><i>Maureen Gibbons</i></u> </td> </tr> </table>		☒ Authorization to charge the total fees indicated above. ☒ (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.	IPEA/US _____ Deposit Account No.: <u>19-3880</u> Date: <u>October 23, 2002</u> Name: <u>Maureen Gibbons</u> Signature: <u><i>Maureen Gibbons</i></u>						
☒ Authorization to charge the total fees indicated above. ☒ (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.	IPEA/US _____ Deposit Account No.: <u>19-3880</u> Date: <u>October 23, 2002</u> Name: <u>Maureen Gibbons</u> Signature: <u><i>Maureen Gibbons</i></u>								

581

The purpose of the fee calculation sheet is to help the applicant to identify the prescribed fees and to calculate the amounts to be paid. It is strongly recommended that the applicant complete, by entering the appropriate amounts in the boxes provided, and submit the fee calculation sheet at the time of filing of the demand. This will help the International Preliminary Examining Authority (IPEA) to verify the calculations and to identify any error in them.

CALCULATION OF PRESCRIBED FEES

Two fees must be paid for international preliminary examination:

- (i) the preliminary examination fee for the benefit of the IPEA (Rule 58.1);
- (ii) the handling fee for the benefit of the International Bureau (Rule 57).

Both fees must be paid to the IPEA within one month from the date on which the demand is submitted. The amount payable is the amount applicable on the date of submittal (Rules 57.3 and 58.1(b)). The fees must be paid in a currency acceptable to the IPEA.

Information about the amount of those fees or about equivalent amounts in other currencies can be obtained from the IPEA or the receiving Office. This information is also published in the *PCT Applicant's Guide, Volume I/B, Annex E*, and from time to time in Section IV of the *PCT Gazette*.

Box P: The amount of the preliminary examination fee must be entered in Box P.

Box H: The amount of the handling fee must be entered in Box H.

Reduction of the Handling Fee for Applicants from Certain States: An applicant who is a natural person and who is a national of and resides in a State whose per capita national income is below 3,000 US dollars (according to the average per capita national income figures used by the United Nations for determining its scale of assessments for the contributions payable for the years 1995, 1996 and 1997) is entitled, in accordance with the Schedule of Fees, to a reduction of 75% of certain PCT fees including the handling fee. If there are several applicants, each must satisfy the above-mentioned criteria. The reduction of the handling fee will be automatically available to any applicant (or applicants) who is (or are) so entitled on the basis of the indications of name, nationality and residence given in Box No. II of the demand.

The fee reduction will be available even if one or more of the applicants are not from PCT Contracting States, provided that each of them is a national and resident of a State that meets the above-mentioned requirements and that at least one of the applicants is a national or resident of a PCT Contracting State and thus is entitled to file an international application.

Natural persons who are nationals of and reside in the following PCT Contracting States are eligible: AL Albania, AM Armenia, AZ Azerbaijan, BA Bosnia and Herzegovina, BF Burkina Faso, BG Bulgaria, BJ Benin, BR Brazil,

BY Belarus, BZ Belize, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, CN China, CO Colombia, CR Costa Rica, CU Cuba, CZ Czech Republic, DM Dominica, DZ Algeria, EC Ecuador, EE Estonia, GA Gabon, GD Grenada, GE Georgia, GH Ghana, GM Gambia, GN Guinea, GW Guinea-Bissau, HR Croatia, HU Hungary, ID Indonesia, IN India, KE Kenya, KG Kyrgyzstan, KP Democratic People's Republic of Korea, KZ Kazakhstan, LC Saint Lucia, LK Sri Lanka, LR Liberia, LS Lesotho, LT Lithuania, LV Latvia, MA Morocco, MD Republic of Moldova, MG Madagascar, MK The former Yugoslav Republic of Macedonia, ML Mali, MN Mongolia, MR Mauritania, MW Malawi, MX Mexico, MZ Mozambique, NE Niger, PL Poland, RO Romania, RU Russian Federation, SD Sudan, SK Slovakia, SL Sierra Leone, SN Senegal, SZ Swaziland, TD Chad, TG Togo, TJ Tajikistan, TM Turkmenistan, TR Turkey, TZ United Republic of Tanzania, UA Ukraine, UG Uganda, UZ Uzbekistan, VN Viet Nam, YU Yugoslavia, ZA South Africa and ZW Zimbabwe. As far as other States are concerned, inquiries should be addressed to the International Bureau.

Calculation of the Handling Fee in Case of Fee Reduction: Where the applicant is (or all applicants are) entitled to a reduction of the handling fee, the total to be entered at Box H is 25% of the handling fee.

Total Box: The total of the amounts inserted in Boxes P and H is the amount which must be paid to the IPEA.

MODE OF PAYMENT

In order to help the IPEA identify the mode of payment of the prescribed fees, it is recommended to mark the applicable check-box(es).

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

The applicant should check whether the IPEA allows the use of deposit accounts for payment of PCT fees. In addition, it is recommended that the applicant check what are the specific conditions applicable to the use of deposit accounts with the IPEA since not all IPEAs provide the same services.

Finally, if the IPEA is not the same national Office or intergovernmental organization as that with which the international application was filed, the deposit account with the receiving Office cannot be charged for the purpose of paying the preliminary examination and handling fees due to the IPEA.

The IPEA will not charge fees to deposit accounts unless the deposit account authorization is signed and indicates the deposit account number.

P. IENT COOPERATION TREA. Y

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

GIBBONS, Maureen
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

14 June 2002 (14.06.02)

Applicant's or agent's file reference

LD227

IMPORTANT NOTIFICATION

International application No.

PCT/US02/09402

International filing date (day/month/year)

26 March 2002 (26.03.02)

International publication date (day/month/year)

Not yet published

Priority date (day/month/year)

28 March 2001 (28.03.01)

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office

Date of receipt
of priority document

28 Marc 2001 (28.03.01)

60/279,327

May 2002 (08.05.02)

BMS PATENT LAW

JUN 25 2002

Docketed item _____

Due Date _____

Attorney _____

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Sylvaine DESCLOUX

Telephone No. (41-22) 338.83.38

**TRANSMITTAL LETTER TO THE
UNITED STATES RECEIVING OFFICE**

Date	26 March 2002
International Application No.	the
Attorney Docket No.	LD227

I. Certification under 37 CFR 1.10 (if applicable)

EL825205727US

EL 825205727 US
Express Mail mailing number

26 March 2002
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

<i>Maureen Gibbons</i>
Signature of person mailing correspondence

Maureen Gibbons
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	NOVEL TYROSINE KINASE INHIBITORS
-------	----------------------------------

Earliest priority date (Day/Month/Year)
28 March 2001

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☒ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.	60/279,327	filed on	28 March 2001 (28.03.01)
application no.		filed on	

- D. ☐ The present international application ☐ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.
- E. ☒ The present international application ☒ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages VARIOUS and ☒ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☒ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

Priority document		Priority document	
-------------------	--	-------------------	--

- E. ☒ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

- V. ☒ Other (please specify): PCT - Easy diskette with request and abstract

The person signing this form is the:

☐ Applicant
☒ Attorney/Agent (Reg. No.) 38,097
☐ Common Representative

BRISTOL-MYERS SQUIBB CO.
Typed name of signatory
Maureen Gibbons
Signature

PCT REQUEST

Original (for SUBMISSION) - printed on 28.03.2002 08:31:30 AM

LD227

584

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	LD227
I	Title of invention	NOVEL TYROSINE KINASE INHIBITORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	WITTMAN, Mark, D.
III-1-5	Address:	30 Fairlawn Dr. Wallingford, CT 06492 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

PCT REQUEST

Original (for SUBMISSION) - printed on 28.03.2002 08:31:30 AM

LD227

585

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BALASUBRAMANIAN, Neelakantan
III-2-5	Address:	26 Horsebarn Lane Madison, CT 06443 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	VELAPARTHI, Upender
III-3-5	Address:	1298 Hartford Turnpike #9J North Haven, CT 06422 United States of America
III-3-6	State of nationality	IN
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	ZIMMERMANN, Kurt
III-4-5	Address:	5 Skeetfield Point Rd. Durham, CT 06422 United States of America
III-4-6	State of nationality	AT
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	SAULNIER, Mark, G.
III-5-5	Address:	34 Ponsett Rd. Higganum, CT 06441 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US
III-6	Applicant and/or inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	LIU, Peiying
III-6-5	Address:	228 Devonshire Lane Madison, CT 06443 United States of America
III-6-6	State of nationality	CA
III-6-7	State of residence	US

PCT REQUEST

3/7

LD227

Original (for SUBMISSION) - printed on 28.03.2002 08:31:30 AM

586

III-7	Applicant and/or inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	SANG, Xiaopeng
III-7-5	Address:	45 Hawthorne Mead Dr. Glastonbury, CT 06033 United States of America
III-7-6	State of nationality	CN
III-7-7	State of residence	US
III-8	Applicant and/or inventor	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	FRENHESON, David, B.
III-8-5	Address:	164 Conrad St. Naugatuck, CT 06770 United States of America
III-8-6	State of nationality	US
III-8-7	State of residence	US
III-9	Applicant and/or inventor	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	STOFFAN, Karen, M.
III-9-5	Address:	149 Whitney St. Hartford, CT 06105 United States of America
III-9-6	State of nationality	US
III-9-7	State of residence	US
III-10	Applicant and/or inventor	
III-10-1	This person is:	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	TARRANT, James, G.
III-10-5	Address:	156 Handy Rd. Hamden, CT 06518 United States of America
III-10-6	State of nationality	US
III-10-7	State of residence	US

PCT REQUEST

Original (for SUBMISSION) - printed on 28.03.2002 08:31:30 AM

LD227

587

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	GIBBONS, Maureen
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-3453
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	44,121
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	ALGIERI, Aldo (31,697); BARAJKO, Suzanne (32,880); BABCOCK, Timothy (39,097); BUCHHOLE, Briana (39,123); D'AMICO, Stephen (46,652); DUBOFF, Samuel (25,969); FURMAN, Theodore (30,942); WILK-ORESCAN, Rosemarie (45,220); HERMENAUI, Ronald (34,620); KILCOYNE, John (33,100); KLEIN, Christopher (34,363); LANGE, Keith (44,201); MAKUJINA, Shah (41,174); MORSE, David (25,742); PATEL, Rana (41,412); DAVIS, Stephen (26,693); PROVOOST, Jonathan (44,292); RODNEY, Burton (22,076); RYAN, Richard (30,491); SHER, Andrey (39,024); SWITZER, Joan (34,740); PEIST, Kenneth (45,006); O'BRIEN, Maureen (42,043); WINSLOW, Anastasia (40,875); BELFIELD, Jing (45,914); FERGUSON, Blair, Q. (34,329); LARSEN, Scott, K. (38,532); VANATTEN, Mary, K. (39,408); DOLAN, Peter, L. (46,307)

PCT REQUEST

5/7

Original (for SUBMISSION) - printed on 28.03.2002 08:31:30 AM

LD227

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GE GM KE LS MW ME SD SL SZ TZ UG ZM EW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AE BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BE CA CH&LI CN CO CR CU CE DE DK DM DE EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KE LC LK LR LS LT LU LV MA MD MG MK MN MW MX ME NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-3 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-4	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	28 March 2001 (28.03.2001)
VI-1-2	Number	60/279,327
VI-1-3	Country	US

598

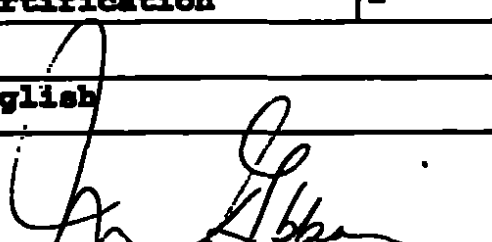
PCT REQUEST

6/7

Original (for SUBMISSION) - printed on 26.03.2002 08:31:30 AM

LD227

589

VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	7	-
IX-2	Description	220	-
IX-3	Claims	27	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	255	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-6	Fee calculation sheet	✓	-
IX-8	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Certification	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	GIBBONS, Maureen	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	

PCT REQUEST

7/7

Original (for SUBMISSION) - printed on 28.03.2002 08:31:30 AM

LD227

590

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmitted of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 26.03.2002 08:31:30 AM

LD227

(This sheet is not part of and does not count as a sheet of the International application)

591

0	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared using b	PCT-EASY Version 2.92 (updated 01.01.2002)		
0-8	Applicant's or agent's file reference	LD227		
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY, et al.		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee T	⇒	240	
12-2-1	Search fee S	⇒	700	
12-2-2	International search to be carried out by	US		
12-3	International fee			
	Basic fee (first 30 sheets) b1	407		
12-4	Remaining sheets	225		
12-5	Additional amount (X)	9.		
12-6	Total additional amount b2	2,025		
12-7	b1 + b2 = B	2,432		
12-8	Designation fees			
	Number of designations contained in International application	93		
12-9	Number of designation fees payable (maximum 5)	5		
12-10	Amount of designation fee (X)	88		
12-11	Total designation fees D	440		
12-12	PCT-EASY fee reduction R	-125		
12-13	Total International fee (B+D-R) I	⇒	2,747	
12-14	Fee for priority document			
	Number of priority documents requested	1		
12-15	Fee per document (X)	15		
12-16	Total priority document fee P	⇒	15	
12-17	TOTAL FEES PAYABLE (T+S+H+P)	⇒	3,702	
12-18	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions			
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.	✓		

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 26.03.2002 08:31:30 AM

LD227

592

12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19-3680
12-22	Date	26 March 2002 (26.03.2002)
12-23	Name and signature	GIBBONS, Maureen 

VALIDATION LOG AND REMARKS

13-1-1	Applicant remarks	[CHEMICAL DRAWING]
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-10	Validation messages Annotate	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

PCT POWER OF ATTORNEY

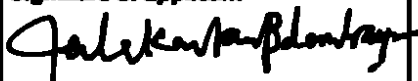
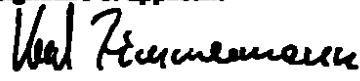
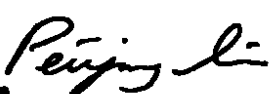
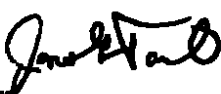
1/2

Printed on 11.02.2002 02:28:29 PM

LD227

593

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
1	The undersigned applicant(s)	WITTMAN, Mark, D.; BALASUBRAMANIAN, Neelakantan; VELAPARTHI, Upender; ZIMMERMANN, Kurt; SAULNIER, Mark, G.; LIU, Peiying; SANG, Xiaopeng; FRENNESSON, David, B.; STOFFAN, Karen, M.; TARRANT, James, G.
1-1-1	hereby appoints (appoint) the following person	GIBBONS, Maureen; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana; D'AMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; HERMENAU, Ronald; KILCOYNE, John; KLEIN, Christopher; FURMAN, Theodore; LANGE, Keith; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rana; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; LOPEZ, Gabriel; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia BRISTOL-MYERS SQUIBB CO. P.O. BOX 4000, Lawrenceville-Princeton Rd. Princeton, NJ 08543 United States of America
1-1-2	hereby appoints (appoint) the following person	ALGIERI, Aldo BRISTOL-MYERS SQUIBB CO. P.O. BOX 4000, Lawrenceville-Princeton Rd. Princeton, NJ 08543 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the international application identified below:	
1-4-1	Title of the invention	NOVEL TYROSINE KINASE INHIBITORS
1-4-2	Applicant's or agent's file reference	LD227
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)

1-5	and to make or receive payments on behalf of the undersigned.	
2-2	Signature of applicant 	
2-2-1	Name	WITTMAN, Mark, D.
2-3	Signature of applicant 	
2-3-1	Name	BALASUBRAMANIAN, Neelakantan
2-4	Signature of applicant 	
2-4-1	Name	VELAPARTHI, Upender
2-5	Signature of applicant 	
2-5-1	Name	ZINGERMANN, Kurt
2-6	Signature of applicant	
2-6-1	Name 	SAULNIER, Mark, G.
2-7	Signature of applicant 	
2-7-1	Name	LIU, Peiying
2-8	Signature of applicant	
2-8-1	Name 	SANG, Xiaopeng
2-9	Signature of applicant	
2-9-1	Name 	FRENNESSON, David, B.
2-10	Signature of applicant 	
2-10-1	Name	STOFFAN, Karen, M.
2-11	Signature of applicant 	
2-11-1	Name	TARRANT, James, G.
3	Date	11 February 2002 (11.02.2002)

PCT POWER OF ATTORNEY

1/2

Printed on 08.02.2002 08:50:00 AM

LD227

595

0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 80.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	GIBBONS, Maureen; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana; D'AMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; HERMENAU, Ronald; KILCOYNE, John; KLEIN, Christopher; FURMAN, Theodore; LANGE, Keith; MAKIJIMA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rana; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; LOPEZ, Gabriel; RYAN, Richard; SHER, Andrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia BRISTOL-MYERS SQUIBB CO. P.O. BOX 4000, Lawrenceville-Princeton Rd. Princeton, NJ 08543 United States of America
1-1-2	hereby appoints (appoint) the following person	ALGIERI, Aldo BRISTOL-MYERS SQUIBB CO. P.O. BOX 4000, Lawrenceville-Princeton Rd. Princeton, NJ 08543 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the International application identified below:	
1-4-1	Title of the invention	NOVEL TYROSINE KINASE INHIBITORS
1-4-2	Applicant's or agent's file reference	LD227
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

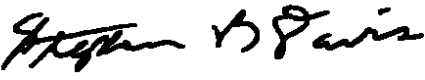
176

PCT POWER F ATTORNEY

Printed on 08.02.2002 08:50:00 AM

LD227

596

2-1	Signature of applicant	
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Stephen B. Davis
2-1-3	Capacity	Patent Counsel
3	Date	08 February 2002 (08.02.2002)

CERTIFICATION

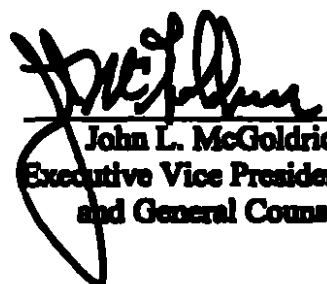
597

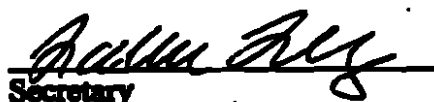
The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Stephen B. Davis
Christopher Klein
Suzanne Babajko
Theodore Furman
David M. Morse
Richard Ryan
Blair Q. Ferguson

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries to or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 25th day of *Jan* 2002.


John L. McGoldrick
Executive Vice President
and General Counsel


Secretary

Original (for SUBMISSION) - printed on 26.03.2002 08:31:30 AM

PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

Green?	Contents The international application contains no drawings. Please verify.
Green?	Payment Please ensure that you have a valid deposit account with the receiving Office selected.
Green?	Annotate All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

Before submitting the International Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form and item 12-23 of the Annex to the Request form have been signed;
- all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the international Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

599

03 085892

SUPERINDUSTRIA Y COMERCIO SISTEMA DE REGISTRO

Fecha 04/11/2003

MANTENIMIENTO DE PROTOCOLOS

Numero : 19358

Fecha : 07/05/1999

Conferido: BRISTOL-MYERS SQUIBB COMPANY

Pais : US ESTADOS UNIDOS DE AMERICA

Ciudad : 82 PRINCETON, NEW JERSEY

Represent: S Sustituir: S Desistir: S

No. Radicacion : 03 085892 Clase: 0 Seev: 0 Seac: 0

Isencia		Codigo	Ctr	Nombre
1	340	A		CASTRO DUQUE RAMIRO
2	3002			GOMEZ MEJIA HECTOR

Encontrados (1/1) registro(s)

50
600

Superintendencia y Dirección
Radicación : 03005892 00000000
Fecha (GEM) : 2003-09-26 17:05:43
Trámite : 011 PET-PATENT 379 FASE INCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 571

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	()
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()		
INCOMPLETA ()		
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()		
INCOMPLETA ()		
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()		
INCOMPLETA ()		

Firma Responsable:

Andrés Rosé

Fecha:



324
601

2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
BRISTOL MYERS SQUIBB COMPANY

Oficio N° 01238

ASUNTO:	Radicación N°	03 085892
	Solicitud internacional	PCT/US2002/08402
	Fecha inicio fase nacional	28/10/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la traducción de las reivindicaciones tal como fueron modificadas. (Numeral 5.2.5, capítulo quinto del título décimo de la Circular Única de la SIC).
- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPÉDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, _____

06 FEB. 2004