06-125963

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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División de Nuevas Creaciones

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SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 06-125963

54. **TITULO** HETEROCICLICOS DE CINCO MIEMBROS UTILES COMO INHIBIDORES DE LA SERINA PROTEASA

51. **CLASIFICACION INTERNACIONAL**

71. **SOLICITANTE** BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON NEW JERSEY ESTADOS UNIDOS DE AMERICA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.**

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SUPERINTENDENCIA

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Fec: 2006-12-15 16:24:39 Usu: ZRUIZ
Rec. 11 PATENTES
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Act 411 PRESENTACION Hdps: 013

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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, Route 206 and Province Line Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21, Torre B, Piso 4 Teléfono: 744-2200 Fax: 742-2200 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre:** Jon J. HANGELAND, Mimi L. QUAN, Joanne M. SMALLHEER, Gregory S. BISACCHI, James R. CORTE, Todd J. FRIENDS, Zhong SUN, Karen A. ROSSI, Cullen L. CAVALLARO **Dirección:** 234 Louise Drive, Morrisville, Pennsylvania 19067 (US); 1437 Innis Lane, Yardley, Pennsylvania 19067 (US); 709 Wynnewood Drive, Yardley, Pennsylvania 19067 (US); 72 Lincoln Street #34, Newton Highlands, Massachusetts 02461 (US); 11 Abella Court, Lawrenceville, New Jersey 08648 (US); 248 Birch Hollow Drive, Bordentown, New Jersey 08505 (US); 11 Coventry Lane, Hopewell, New Jersey 08525 (US); 2084 Farmview Drive, Newton, Pennsylvania 18940 (US); 3 Westbury Court, Robbinsville, New Jersey 08691 (US), (Respectivamente). **Nacionalidad o Domicilio:** Estados Unidos de América (Respectivamente)	

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

2020-F06 (01-11-15)

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar 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.
- [x] Otros: Documentos PCT
  Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA: _____

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
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C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE :

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

4

PATENTE [X] PCT/US2005/021212 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON NEW JERSEY ESTADOS UNIDOS DE AMERICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO HETEROCICLICOS DE CINCO MIEMBROS UTILES COMO INHIBIDORES DE LA SERINA PROTEASA

CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) JON J HANGELAND MIMI L QUAN JOANNE M SMALLHEER GREGORY S BISACCHI

OTROS JAMES R CORTE TODD J FRIENDS ZHONG SUN KAREN A ROSSI CULLEN L CAVALLARO

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(71) Applicant *(for all designated States except US)*: BRISTOL-MYERS SQUIBB COMPANY [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HANGELAND, Jon J. [US/US]; 234 Louise Drive, Morrisville, Pennsylvania 19067 (US). QUAN, Mimi L. [US/US]; 1437 Innis Lane, Yardley, Pennsylvania 19067 (US). SMALLHEER, Joanne M. [US/US]; 709 Wynnewood Drive, Yardley, Pennsylvania 19067 (US). BISACCHI, Gregory S. [US/US]; 72 Lincoln Street #34, Newton Highlands, Massachusetts 02461 (US). CORTE, James R. [US/US]; 11 Abelia Court, Lawrenceville, New Jersey 08648 (US). FRIENDS, Todd J. [US/US]; 246 Birch Hollow Drive, Bordentown, New Jersey 08505 (US). SUN, Zhong [US/US]; 11 Coventry Lane, Hopewell, New Jersey 08525 (US). ROSSI, Karen A. [US/US]; 2084 Farmview Drive, Newton, Pennsylvania 18940 (US). CAVALLARO, Cullen L. [US/US]; 3 Westbury Court, Robbinsville, New Jersey 08691 (US).

(74) Agents: SUN, Jing G. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

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

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

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

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

(54) Title: FIVE-MEMBERED HETEROCYCLES USEFUL AS SERINE PROTEASE INHIBITORS

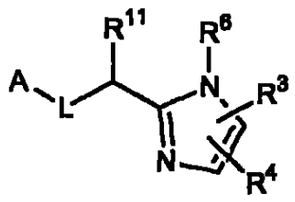
(57) Abstract: The present invention provides a method for treating a thrombotic or an inflammatory disorder administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I) or Formula (V): (I) [INSERTCHEMICAL STRUCTURE HERE] (V)[INSERT CHEMICAL STRUCTURE HERE] or a stereoisomer or pharmaceutically acceptable salt or solvate form thereof, wherein the variables A, L, Z, R3, R4, R6, R11, X1, X2, and X3 are as defined herein. The compounds of Formula (I) are useful as selective inhibitors of serine protease enzymes of the coagulation cascade and/or contact activation system; for example thrombin, factor Xa, factor XIa, factor IXa, factor VIIa and/or plasma kallikrein. In particular, it relates to compounds that are selective factor XIa inhibitors. This invention also provides compounds within the scope of Formula I and relates to pharmaceutical compositions comprising these compounds.

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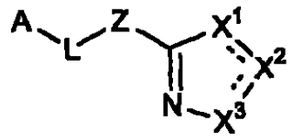
FIVE-MEMBERED HETEROCYCLES USEFUL AS SERINE PROTEASE INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention provides a method for treating a thrombotic or an inflammatory disorder administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I) or Formula (V):



(I)



(V)

or a stereoisomer or pharmaceutically acceptable salt or solvate form thereof, wherein the variables A, L, Z, R^3, R^4, R^6, R^{11}, X^1, X^2, and X^3 are as defined herein. The compounds of Formula (I) are useful as selective inhibitors of serine protease enzymes of the coagulation cascade and/or contact activation system; for example thrombin, factor Xa, factor XIa, factor IXa, factor VIIa and/or plasma kallikrein. In particular, it relates to compounds that are selective factor XIa inhibitors or dual inhibitors of fXIa and plasma kallikrein. This invention also relates to pharmaceutical compositions comprising these compounds and methods of using the same.

BACKGROUND OF THE INVENTION

[0002] Factor XIa is a plasma serine protease involved in the regulation of blood coagulation. While blood coagulation is a necessary and important part of the regulation of an organism's homeostasis, abnormal blood coagulation can also have deleterious effects. For instance, thrombosis is the formation or presence of a blood clot inside a blood vessel or cavity of the heart. Such a blood clot can lodge in a blood vessel blocking circulation and inducing a heart attack or stroke. Thromboembolic disorders are the largest cause of mortality and disability in the industrialized world.

[0003] Blood coagulation is initiated *in vivo* by the binding of tissue factor (TF) to Factor VII (FVII) to generate Factor VIIa (FVIIa). The resulting TF:FVIIa

complex activates Factor IX (FIX) and Factor X (FX) which leads to the production of Factor Xa (FXa). The FXa that is generated catalyzes the transformation of prothrombin into small amounts of thrombin before this pathway is shut down by tissue factor pathway inhibitor (TFPI). The process of coagulation is then further propagated via the feedback activation of Factors V, VIII and XI by catalytic amounts of thrombin. (Walsh, P. N. *Thromb. Haemostasis*. 1999, *82*, 234-242.) Factor XIa plays a key role in propagating this amplification loop and is thus an attractive target for anti-thrombotic therapy.

[0004] An alternative way of initiation of coagulation is operative when blood is exposed to artificial surfaces (e.g., during hemodialysis, 'on-pump' cardiovascular surgery, vessel grafts, bacterial sepsis). This process is also termed contact activation. Surface absorption of factor XII leads to a conformational change in the factor XII molecule, thereby facilitating activation to proteolytic active factor XII molecules (factor XIIa and factor XIIf). Factor XIIa (or XIIf) has a number of target proteins, including plasma prekallikrein and factor XI. Active plasma kallikrein further activates factor XII, leading to an amplification of contact activation. Contact activation is a surface mediated process responsible in part for the regulation of thrombosis and inflammation, and is mediated, at least in part, by fibrinolytic-, complement-, kininogen/kinin-, and other humoral and cellular pathways (for review, Colcman, R. *Contact Activation Pathway*, pages 103-122 in *Hemostasis and Thrombosis*, Lippincott Williams & Wilkins 2001; Schmaier A.H. *Contact Activation*, pages 105-128 in *Thrombosis and Hemorrhage*, 1998).

[0005] Factor XI is a zymogen of a trypsin-like serine protease and is present in plasma at a relatively low concentration. Proteolytic activation at an internal R369-I370 bond yields a heavy chain (369 amino acids) and a light chain (238 amino acids). The latter contains a typical trypsin-like catalytic triad (H413, D464, and S557). Activation of factor XI by thrombin is believed to occur on negatively charged surfaces, most likely on the surface of activated platelets. Platelets contain high affinity (0.8 nM) specific sites (130-500/platelet) for activated factor XI. After activation, factor XIa remains surface bound and recognizes factor IX as its normal macromolecular substrate. (Galiani, D. *Trends Cardiovasc. Med.* 2000, *10*, 198-204.)

[0006] In addition to the feedback activation mechanisms described above, thrombin activates thrombin activated fibrinolysis inhibitor (TAFI), a plasma carboxypeptidase that cleaves C-terminal lysine and arginine residues on fibrin, reducing the ability of fibrin to enhance tissue-type plasminogen activator (tPA) dependent plasminogen activation. In the presence of antibodies to FXIa, clot lysis can occur more rapidly independent of plasma TAFI concentration. (Bouma, B. N. et al. *Thromb. Res.* 2001, *101*, 329-354.) Thus, inhibitors of factor XIa are expected to be anticoagulant and profibrinolytic.

[0007] Genetic evidence indicates that factor XI is not required for normal homeostasis, implying a superior safety profile of the factor XI mechanism compared to competing antithrombotic mechanisms. In contrast to hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency), mutations of the factor XI gene causing factor XI deficiency (hemophilia C) result in only a mild to moderate bleeding diathesis characterized primarily by postoperative or posttraumatic, but rarely spontaneous hemorrhage. Postoperative bleeding occurs mostly in tissue with high concentrations of endogenous fibrinolytic activity (*e.g.*, oral cavity, and urogenital system). The majority of the cases are fortuitously identified by preoperative prolongation of APTT (intrinsic system) without any prior bleeding history.

[0008] The increased safety of inhibition of XIa as an anticoagulation therapy is further supported by the fact that Factor XI knock-out mice, which have no detectable factor XI protein, undergo normal development, and have a normal life span. No evidence for spontaneous bleeding has been noted. The APTT (intrinsic system) is prolonged in a gene dose-dependent fashion. Interestingly, even after severe stimulation of the coagulation system (tail transection), the bleeding time is not significantly prolonged compared to wild-type and heterozygous litter mates. (Gailiani, D. *Frontiers in Bioscience* 2001, *6*, 201-207; Gailiani, D. et al. *Blood Coagulation and Fibrinolysis* 1997, *8*, 134-144.) Taken together, these observations suggest that high levels of inhibition of factor XIa should be well tolerated. This is in contrast to gene targeting experiments with other coagulation factors.

[0009] *In vivo* activation of factor XI can be determined by complex formation with either C1 inhibitor or alpha 1 antitrypsin. In a study of 50 patients

with acute myocardial infarction (AMI), approximately 25% of the patients had values above the upper normal range of the complex ELISA. This study can be viewed as evidence that at least in a subpopulation of patients with AMI, factor XI activation contributes to thrombin formation (Minnema, M.C. et al. *Arterioscler. Thromb. Vasc. Biol.* 2000, *20*, 2489-2493). A second study establishes a positive correlation between the extent of coronary arteriosclerosis and factor XIa in complex with alpha 1 antitrypsin (Murakami, T. et al. *Arterioscler Thromb Vasc Biol* 1995, *15*, 1107-1113.). In another study, Factor XI levels above the 90th percentile in patients were associated with a 2.2-fold increased risk for venous thrombosis (Meijers, J.C.M. et al. *N. Engl. J. Med.* 2000, *342*, 696-701.).

[0010] Plasma kallikrein is a zymogen of a trypsin-like serine protease and is present in plasma at 35 to 50 μg/mL. The gene structure is similar to that of factor XI, overall, the amino acid sequence of plasma kallikrein has 58% homology to factor XI. Proteolytic activation by factor XIIa at an internal I 389- R390 bond yields a heavy chain (371 amino acids) and a light chain (248 amino acids). The active site of kallikrein is contained in the light chain. The light chain of plasma kallikrein reacts with protease inhibitors, including alpha 2 macroglobulin and C1- inhibitor. Interestingly, heparin significantly accelerates the inhibition of plasma kallikrein by antithrombin III in the presence of high molecular weight kininogen (HMWK). In blood, the majority of plasma kallikrein circulates in complex with HMWK. Kallikrein cleaves HMWK to liberate bradykinin. Bradykinin release results in increase of vascular permeability and vasodilation (for review, Coleman, R. *Contact Activation Pathway*, pages 103-122 in *Hemostasis and Thrombosis*, Lippincott Williams & Wilkins 2001; Schmaier A.H. *Contact Activation*, pages 105-128 in *Thrombosis and Hemorrhage*, 1998).

[0011] Proteins or peptides that reportedly inhibit Factor XIa are disclosed in WO 01/27079. There are advantages in using small organic compounds, however, in preparing pharmaceuticals, *e.g.*, small compounds generally have better oral bioavailability and compatibility in making formulations to aid in delivery of the drug as compared with large proteins or peptides. Small molecule inhibitors of Factor XIa are disclosed in U.S. Patent Application Publication US20040235847A1 and US Patent Application Publication US20040220206A1.

[0012] Moreover, it is also desirable to find new compounds with improved pharmacological characteristics compared with known serine protease inhibitors. For example, it is preferred to find new compounds with improved factor XIa inhibitory activity and selectivity for factor XIa versus other serine proteases. Also, it is preferred to find new compounds with improved plasma kallikrein inhibitory activity and selectivity for plasma kallikrein versus other serine proteases. It is also desirable and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to: (a) pharmaceutical properties; (b) dosage requirements; (c) factors which decrease blood concentration peak-to-trough characteristics; (d) factors that increase the concentration of active drug at the receptor; (e) factors that decrease the liability for clinical drug-drug interactions; (f) factors that decrease the potential for adverse side-effects; and (g) factors that improve manufacturing costs or feasibility.

SUMMARY OF THE INVENTION

[0013] The present invention provides novel five-membered heterocycle derivatives, and analogues thereof, which are useful as selective inhibitors of serine protease enzymes, especially factor XIa and/or plasma kallikrein, or stereoisomers or pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[0014] The present invention also provides processes and intermediates for making the compounds of the present invention or a stereoisomer or a pharmaceutically acceptable salt, solvate, or prodrug form thereof.

[0015] The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt, solvate or prodrug form thereof.

[0016] The present invention also provides a method for modulation of the coagulation cascade and/or the contact activation system comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug form thereof.

[0017] The present invention also provides a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug form thereof.

[0018] The present invention also provides a method for treating inflammatory diseases disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug form thereof.

[0019] The present invention also provides novel five-membered heterocycle derivatives, and analogues thereof, for use in therapy.

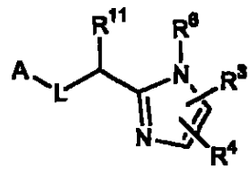
[0020] The present invention also provides the use of five-membered heterocycle derivatives, and analogues thereof, for the manufacture of a medicament for the treatment of a thromboembolic disorder.

[0021] The present invention also provides the use of five-membered heterocycle derivatives, and analogues thereof, for the manufacture of a medicament for the treatment of an inflammatory disorder.

[0022] These and other embodiments, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that the presently claimed novel compounds of the present invention, or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor XIa inhibitors and/or plasma kallikrein inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

[0023] In a first aspect, the present invention includes, *inter alia*, a compound of Formula (I):



(I)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein:

[0024] A is C_{3-10} carbocycle substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 12-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2; provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

[0025] L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, or $-C(O)CH_2-$;

[0026] R^1 is, independently at each occurrence, $-NH_2$, $-NH(C_1-C_3$ alkyl), $-N(C_1-C_3$ alkyl$)_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7CO_2R^a$, $-CH_2NH_2$, $-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl$)_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(C_1-C_3$ alkyl), $-CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $-CH(C_{1-4}$ alkyl$)NH_2$, $-C(C_{1-4}$ alkyl$)_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-cyclopropyl, or C_{1-6} alkyl substituted with 0-1 R^{1a};

[0027] R^{1a} is H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p-C_{1-4}$ alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

[0028] R^2 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{2a}, C_{2-6} alkenyl substituted with 0-2 R^{2a}, C_{2-6} alkynyl substituted with 0-2 R^{2a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{2b}, or $-(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{2b};

[0029] R^{2a} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[0030] R^{2b} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[0031] alternately, when R^1 and R^2 groups are substituted on adjacent ring atoms, they can be taken together with the ring atoms to which they are attached to form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said carbocycle or heterocycle is substituted with 0-2 R^{2b};

[0032] R^3 is $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[0033] R^{3a} is, independently at each occurrence, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, -C(O)-C_1-C_4 alkyl, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, C_1-4 haloalkyl, C_1-4 haloalkoxy-, C_1-6 alkyl substituted by R^{3d}, C_2-6 alkenyl substituted by R^{3d}, C_2-6 alkynyl substituted by R^{3d}, C_3-6 cycloalkyl substituted by 0-1 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or -$(CH_2)_r$–5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[0034] alternately, when two R^{3a} groups are located on adjacent atoms, they can be taken together with the atoms to which they are attached to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[0035] R^{3b} is, independently at each occurrence, H, C_1-6 alkyl substituted with 0-2 R^{3d}, C_2-6 alkenyl substituted with 0-2 R^{3d}, C_2-6 alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or -$(CH_2)_r$–5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[0036] R^{3c} is, independently at each occurrence, C_1-6 alkyl substituted with 0-2 R^{3d}, C_2-6 alkenyl substituted with 0-2 R^{3d}, C_2-6 alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or -$(CH_2)_r$–5- to 10-

membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[0037] R^{3d} is, independently at each occurrence, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_pR^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, C_{2-6} alkynyl substituted with 0-2 R^e, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[0038] R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{4b}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[0039] R^{4a} is, independently at each occurrence, H, F, =O, C_{1-6} alkyl, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[0040] R^{4b} is, independently at each occurrence, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[0041] alternately, R^3 and R^4 groups when located on adjacent atoms, can be taken together to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-

membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[0042] R^6 is H;

[0043] R^7 is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n-C_{3-10}$ carbocycle, $-(CH_2)_n-$(5-10 membered heteroaryl), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{1-4}$ alkyl), or $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{6-10}$ aryl); wherein said alkyl, carbocycle, heteroaryl, and aryl are optionally substituted with 0-2 R^f;

[0044] R^8 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_r-$phenyl, or $-(CH_2)_n-$5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said alkyl, phenyl and heterocycle are optionally substituted with 0-2 R^f;

[0045] alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[0046] R^{8a} is, independently at each occurrence, H, OH, C_{1-6} alkyl, C_{1-4} alkoxy, (C_{6-10} aryl)-C_{1-4} alkoxy, $-(CH_2)_n-$phenyl, $-(CH_2)_n-$(5-10 membered heteroaryl), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{1-4}$ alkyl), or $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{6-10}$ aryl); wherein said phenyl, aryl, and heteroaryl is optionally substituted with 0-2 R^f;

[0047] R^9 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_r-$phenyl; wherein said alkyl and phenyl are optionally substituted with 0-2 R^f;

[0048] R^{9a} is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n-$phenyl;

[0049] alternatively, R^8 and R^9, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2

additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[0050] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, C_{2-6} alkenyl substituted with 0-3 R^{10a}, C_{2-6} alkynyl substituted with 0-3 R^{10a}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[0051] R^{10a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[0052] R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CR^{14}R^{15})_r-C_{3-10}$ carbocycle substituted with 0-3 R^{11b}, or $-(CR^{14}R^{15})_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b};

[0053] R^{11a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, CF_3, SR^a, F, CN, NO_2, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^c$, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^d;

[0054] R^{11b} is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-,

$-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[0055] alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R^g;

[0056] R^{14} and R^{15} are, independently at each occurrence, H, F, or C_{1-4} alkyl;

[0057] alternately, R^{14} combines with R^{15} to form =O;

[0058] R^a is, independently at each occurrence, H, CF_3, C_{1-6} alkyl, $-(CH_2)_r-C_{3-7}$ cycloalkyl, $-(CH_2)_r-C_{6-10}$ aryl, or $-(CH_2)_r$-5- to 10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said cycloalkyl, aryl and heterocycle groups are optionally substituted with 0-2 R^f;

[0059] R^b is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[0060] R^c is, independently at each occurrence, CF_3, C_{1-6} alkyl substituted with 0-2 R^f, C_{3-6} cycloalkyl substituted with 0-2 R^f, C_{6-10} aryl, 5- to 10-membered heteroaryl, (C_{6-10} aryl)-C_{1-4} alkyl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl, wherein said aryl and heteroaryl groups are optionally substituted with 0-3 R^f;

[0061] R^d is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, or

C_{2-6} alkynyl substituted with 0-2 R^e;

[0062] R^e is, independently at each occurrence, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

[0063] R^f is, independently at each occurrence, H, =O, $-(CH_2)_r$-OR^g, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-C_{1-4} alkyl, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-(CH_2)_n$-phenyl;

[0064] R^g is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

[0065] n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

[0066] p, at each occurrence, is selected from 0, 1, and 2;

[0067] r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

[0068] s, at each occurrence, is selected from 1, 2, 3, and 4;

[0069] provided that:

[0070] (a). when L is –C(O)NH-, R^3 is not 2,4-dichlorophenyl, 4-nitrophenyl or pentafluorophenyl;

[0071] (b). when L is –C(O)NH-, R^{11} is not $-CH_2$-(3-indolyl), $-(CH_2)_4NHCO_2(t\text{-Bu})$ or $-(CH_2)_4NH_2$.

[0072] In a second aspect, the present invention includes compounds of Formula (I), within the scope of the first aspect wherein:

[0073] L is $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, $-CH_2CONR^{10}$-, or $-NR^{10}COCH_2$-;

[0074] R^3 is $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d},

-$(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, -$(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[0075] R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, -$C(O)R^a$, -$C(O)OR^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_pR^c$, -$S(O)R^c$, -$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[0076] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, -$(CH_2)_r$-phenyl substituted with 0-2 R^d, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

[0077] R^{11} is C_{1-4} haloalkyl, -$(CH_2)_r$-$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{11a}, C_{2-6} alkenyl substituted with 0-2 R^{11a}, C_{2-6} alkynyl substituted with 0-2 R^{11a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or -$(CH_2)_r$-5-to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

[0078] In a third aspect, the present invention includes compounds of Formula (I), within the scope of the first aspect wherein:

[0079] R^1 is, independently at each occurrence, F, Cl, Me, Et, -NH_2, -$C(=NH)NH_2$, -$C(O)NH_2$, -CH_2NH_2, -$CH_2CH_2NH_2$, -CH_2NHCO_2Bn, -$CH_2NHCO_2(t\text{-}Bu)$, -$CH(Me)NH_2$, -$C(Me)_2NH_2$, -NHEt, -$NHCO_2(t\text{-}Bu)$, -$NHCO_2Bn$, -SO_2NH_2, OR^a, or -CH_2R^{1a};

[0080] R^3 is -CO_2H, -CO_2Me, -$C(O)NHCH_2CO_2H$, -$C(O)NHCH_2CO_2Et$,

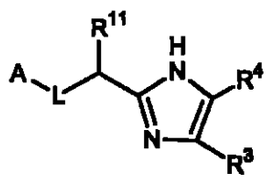
-C(O)NH_2, -C(O)NHMe, -C(O)NHBn, -$(CH_2)_r$-phenyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, naphthyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, indanyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a} and 0-1 R^{3d};

[0081] R^4 is H, F, Cl, Br, CF_3, OMe, NH_2, CO_2H, CO_2Me, CO_2Et, -$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[0082] R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, -$CH_2CH_2CO_2H$, -$CH_2CH_2CO_2Me$, -$CH_2CH_2CO_2Et$, -$CH_2CH_2CONH_2$, or -$CH_2CH_2CONHCH_2CH_2Ph$; and

[0083] R^{11} is C_{1-6} alkyl, -$CH_2CONR^8R^9$, -$CH_2CH_2CONR^8R^9$, -CH_2OBn, -CH_2SBn, -$(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{11b}.

[0084] In a fourth aspect, the present invention includes a compound of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect wherein:

[0085] A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

[0086] L is -C(O)NH- or -NHC(O)-;

[0087] R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

[0088] R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, -C(O)NHMe, -C(O)NHBn, phenyl substituted with 0-2 R^{3a}, naphthyl substituted with 0-2 R^{3a}, indanyl substituted with 0-2 R^{3a}, or a 5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a};

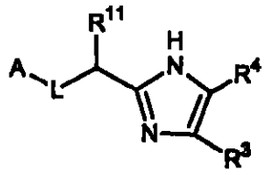
[0089] R^4 is H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{4b};

[0090] R^{11} is C_{1-6} alkyl, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or $-(CH_2)_r$-5- to 10-membered heteroaryl substituted with 0-2 R^{11b} and selected from thiazolyl, oxazolyl, triazolyl, tetrazolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl; and

[0091] R^{11b} is, independently at each occurrence, H, F, Cl, Br, CF_3, OMe, OEt, O(*i*-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, C_1-C_4-alkyl, Ph, or Bn;

[0092] alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R8.

[0093] In a fifth aspect, the present invention includes a compound of Formula (II):

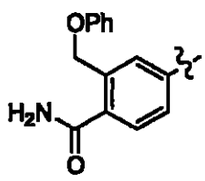
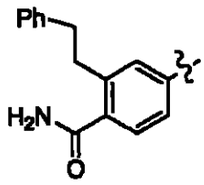
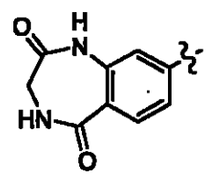


(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect wherein:

[0094] A is 4-CH_2NH_2-cyclohexyl, 4-CO_2Me-cyclohexyl, 4-$CONH_2$-cyclohexyl, 4-$NHCO_2$(*t*-Bu)-cyclohexyl, 4-$NHCO_2$Bn-cyclohexyl, phenyl, 4-Me-phenyl, 3-OMe-phenyl, 4-CH_2NH_2-phenyl, 3-$CONH_2$-phenyl, 4-$CONH_2$-phenyl, 3-amidino-phenyl, 4-amidino-phenyl, 2-F-4-Me-phenyl, 2-Bn-4-CH_2NH_2-phenyl, 4-SO_2NH_2-phenyl, 2-F-5-OMe-phenyl, 2-F-4-Cl-phenyl, 2-F-4-CH_2NH_2-phenyl, 2-F-4-$CONH_2$-phenyl, 2-Cl-4-$CONH_2$-phenyl, 2-Et-4-CH_2NH_2-phenyl, 2-NHEt-4-CH_2NH_2-phenyl, 2-OMe-4-$CONH_2$-phenyl, 3-OMe-4-$CONH_2$-phenyl, 1,2,3,4-tetrahydronaphth-2-yl, 3-Cl-thien-2-yl, indol-5-yl, indol-6-yl, indazol-6-yl, 3-NH_2-indazol-6-yl, 3-NH_2-indazol-5-yl, 1-Me-3-NH_2-indazol-6-yl, 3-NH_2-benzisoxazol-6-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl,

2-COPh-1,2,3,4-tetrahydroisoquinolin-3-yl,
2-CO_2Bn-1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-1-on-6-yl,
2H-isoquinolin-1-on-6-yl, isoquinolin-6-yl, 1-NH_2-isoquinolin-6-yl,
1-NH_2-3-Me-isoquinolin-6-yl, 1-NH_2-5,6,7,8-tetrahydroisoquinolin-6-yl,
4-NH_2-quinazolin-7-yl, 3H-quinazolin-4-on-7-yl,



or

;

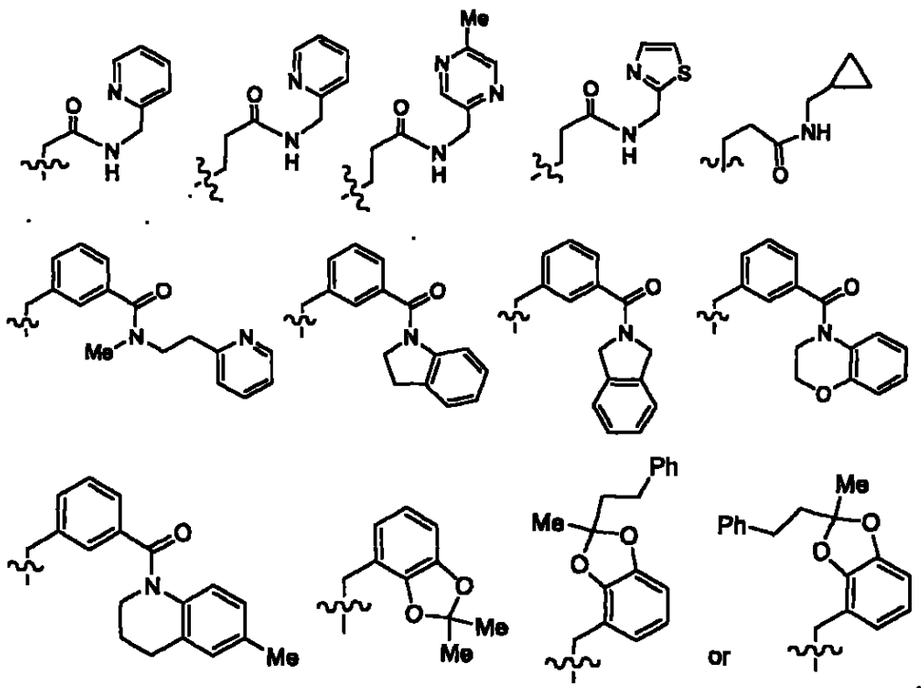
[0095] R^3 is CO_2H, CO_2Me, -C(O)NHCH$_2$CO$_2$H, -C(O)NHCH$_2$CO$_2$Et,
-C(O)NH_2, -C(O)NHMe, -C(O)NHBn, phenyl, phenethyl, -(CH=CH)-phenyl,
3-biphenyl, 4-biphenyl, 3,4-methylenedioxyphenyl, 1-naphthyl, 2-naphthyl,
3-NH_2-phenyl, 3-NMe_2-phenyl, 4-OPh-phenyl, 4-OBn-phenyl,
4-(*t*-butoxymethyl)-phenyl, 4-SO_2Me-phenyl, 3-CN-phenyl, 4-CN-phenyl,
3-F-phenyl, 4-F-phenyl, 3-Cl-phenyl, 4-Cl-phenyl, 3-Br-phenyl, 4-Br-phenyl,
3-OH-phenyl, 4-OH-phenyl, 2-OMe-phenyl, 3-OMe-phenyl, 4-OMe-phenyl,
3-CF_3-phenyl, 4-CF_3-phenyl, 3-CO_2H-phenyl, 4-CO_2H-phenyl, 3-CO_2Me-phenyl,
4-CO_2Me-phenyl, 3-CH_2CO_2H-phenyl, 4-CH_2CO_2H-phenyl,
4-CH_2CO_2Me-phenyl, 3-CH_2CO_2Et-phenyl, 4-CH_2CO_2Et-phenyl,
3-$CONH_2$-phenyl, 4-$CONH_2$-phenyl, 3-CH_2CONH_2-phenyl, 4-CH_2CONH_2-phenyl,
4-CONHMe-phenyl, 4-$CONMe_2$-phenyl, 4-amidino-phenyl, 3-NHCOMe-phenyl,
4-NHCOMe-phenyl, 4-$NHCO_2$Me-phenyl, 4-SO_2NH_2-phenyl, 3-$NHSO_2$Me-phenyl,
4-$NHSO_2$Me-phenyl, 2,4-diF-phenyl, 3-F-4-CN-phenyl, 3-CN-5-F-phenyl,
3-F-4-$CONH_2$-phenyl, 3-CO_2H-4-CN-phenyl, 3-NMe_2-4-CN-phenyl,
3-Ph-4-$CONH_2$-phenyl, 4-(2-oxo-1-piperidino)-phenyl, thiazol-2-yl,
4-CO_2Me-thiazol-2-yl, 4-$CONH_2$-thiazol-2-yl, 1-Bn-pyazol-4-yl, 5-Ph-oxazol-2-yl,
5-$CONH_2$-thien-2-yl, 5-CO_2H-thien-2-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl,
6-NH_2-pyrid-3-yl, benzimidazol-2-yl, 1-Me-benzimidazol-2-yl, benzoxazol-2-yl,
benzothiazol-2-yl, 3-NH_2-benzisoxazol-6-yl, 3-NH_2-benzisoxazol-5-yl, indazol-5-yl,
indazol-6-yl, 3-NH_2-indazol-5-yl, 3-OH-indazol-5-yl, 3-NH_2-indazol-6-yl,

3-NH_2-4-F-indazol-6-yl, 3-NH_2-5-F-indazol-6-yl, 3-NH_2-7-F-indazol-6-yl, 4-imino-3,4-dihydro-2*H*-phthalazin-1-on-7-yl, 3-(5-tetrazolyl)-phenyl, 2,3-dihydro-isoindol-1-on-6-yl, quinolin-5-yl, quinolin-6-yl, quinolin-8-yl, isoquinolin-5-yl, 2H-isoquinolin-1-on-6-yl, 2,4-diaminoquinazolin-7-yl, or 4-NH_2-quinazolin-7-yl;

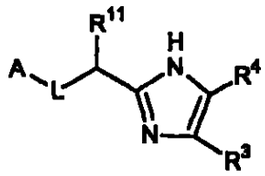
[0096] R^4 is H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, phenyl, 3-F-4-CN-phenyl, or 3-NH_2-6-indazolyl; and

[0097] R^{11} is Me, neopentyl, cyclohexylmethyl, -$CH_2CH_2CONHBn$, -$CH_2CH_2CONH(CH_2CH_2Ph)$, -$CH_2CH_2CON(Me)Bn$, benzyl, phenethyl, 2-Me-benzyl, 3-Me-benzyl, 4-Me-benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl, 2-Cl-benzyl, 3-Cl-benzyl, 4-Cl-benzyl, 2-Br-benzyl, 3-Br-benzyl, 4-Br-benzyl, 3-CF_3-benzyl, 4-CF_3-benzyl, 2-NH_2-benzyl, 3-NH_2-benzyl, 2-NO_2-benzyl, 3-NO_2-benzyl, 4-NO_2-benzyl, 3-OMe-benzyl, 4-OMe-benzyl, 3-OCF_2H-benzyl, 2-OCF_3-benzyl, 3-OCF_3-benzyl, 2-OPh-benzyl, 3-OPh-benzyl, 2-OBn-benzyl, 3-OBn-benzyl, 4-OBn-benzyl, 4-COPh-benzyl, 3-CO_2H-benzyl, 3-CO_2Me-benzyl, 3-NHAc-benzyl, 2-NHCOPh-benzyl, 2-NHCOBn-benzyl, 3-NHCOBn-benzyl, 3-N(Me)COPh-benzyl, 3-(-$NHCOCH_2CH_2Ph$)-benzyl, 2-$NHSO_2Ph$-benzyl, 3-$NHSO_2Ph$-benzyl, 3-[$SO_2N(Me)Ph$]-benzyl, 3-[$N(Me)SO_2Ph$]-benzyl, 3-[CONH(*i*-Bu)]-benzyl, 3-[CONH(*t*-Bu)]-benzyl, 3-[CONH(isopentyl)]-benzyl, 3-[CONH(2-Me-Ph)]-benzyl, 3-[CONH(3-Me-Ph)]-benzyl, 3-[CONH(4-Me-Ph)]-benzyl, 3-[CONH(4-F-Ph)]-benzyl, 3-[CONH(1-naphthyl)]-benzyl, 3-(CONHBn)-benzyl, 3-[CONH(4-Cl-Bn)]-benzyl, 3-[CONH(4-OMe-Bn)]-benzyl, 3-[$CONHCH_2CH_2Ph$]-benzyl, 3-[$CONHCH_2CH_2$(4-OMe-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(2-Cl-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(3-Cl-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(4-Cl-Ph)]-benzyl, 3-[$CONH(CH_2)_3Ph$]-benzyl, 3-[$CONMe_2$]-benzyl, 3-[CON(Me)(Et)]-benzyl, 3-[CON(Me)(*i*-Pr)]-benzyl, 3-[CON(Me)(*i*-Bu)]-benzyl, 3-[CON(Me)Ph]-benzyl, 3-[CON(Me)(3-Me-Ph)]-benzyl, 3-[CON(Me)(4-Me-Ph)]-benzyl, 3-[CON(Me)Bn]-benzyl, 3-[CON(Me)(3-Cl-Bn)]-benzyl, 3-[CON(Me)(4-Cl-Bn)]-benzyl, 3-[$CON(Me)(CH_2CH_2Ph)$]-benzyl,

3-[CON(Et)Ph]-benzyl, 3-[CO(1-piperidino)]-benzyl, 3-[CO(4-Ph-1-piperidino)]-benzyl, 3-[CO(1,2,3,4-tetrahydroisoquinolino)]-benzyl, 2-Ph-benzyl, 3-Ph-benzyl, 4-Ph-benzyl, 3-phenethyl-benzyl, -CH_2OBn, -CH_2SBn, 1-naphthylmethyl, 2-naphthylmethyl, thiazol-4-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, 1-Bn-imidazol-4-ylmethyl, benzothiazol-2-ylmethyl,



[0098] In a sixth aspect, the present invention includes a compound of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect wherein:

[0099] R^3 is 3-NH_2-indazol-5-yl, 3-OH-indazol-5-yl,

3-NH_2-benzisoxazol-6-yl, 3-NH_2-benzisoxazol-5-yl, indazol-5-yl, indazol-6-yl, 3-NH_2-indazol-6-yl, 3-NH_2-4-F-indazol-6-yl, 3-NH_2-5-F-indazol-6-yl, 3-NH_2-7-F-indazol-6-yl, isoquinolin-5-yl, quinolin-5-yl, quinolin-8-yl, 2H-isoquinolin-1-on-6-yl, 2,4-diaminoquinazolin-7-yl, or 4-NH_2-quinazolin-7-yl.

[00100] In a seventh aspect, the present invention includes compounds of Formula (IIa) within the scope of the sixth aspect wherein:

[00101] L is -C(O)NR^{10}- or -NR^{10}C(O)-;

[00102] R^1 is, independently at each occurrence, F, Cl, Me, Et, -NH_2, -C(=NH)NH_2, -C(O)NH_2, -CH_2NH_2, -$CH_2CH_2NH_2$, -CH_2NHCO_2Bn, -CH_2NHCO_2(*t*-Bu), -CH(Me)NH_2, -C(Me)$_2NH_2$, -NHEt, -$NHCO_2$(*t*-Bu), -$NHCO_2$Bn, -SO_2NH_2, OR^a, or -CH_2R^{1a};

[00103] R^4 is H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, -$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00104] R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, -$CH_2CH_2CO_2H$, -$CH_2CH_2CO_2Me$, -$CH_2CH_2CO_2Et$, -$CH_2CH_2CONH_2$, or -$CH_2CH_2CONHCH_2CH_2Ph$;

[00105] R^{11} is C_1-C_6 alkyl, -$CH_2CONR^8R^9$, -$CH_2CH_2CONR^8R^9$, -CH_2OBn, -CH_2SBn, -$(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{11b}; and

[00106] R^{11b} is, independently at each occurrence, H, F, Cl, Br, CF_3, OMe, OEt, O(*i*-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, -NH_2, -C(O)R^a, -C(O)OR^a,

-C(O)NR^7R^8, -$NR^7C(O)R^b$, -$N^8CO_2R^c$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_pR^c$, -SO_2R^c, C_1-C_4-alkyl, Ph, or Bn.

[00107] In an eighth aspect, the present invention includes compounds of Formula (II), within the scope of the seventh aspect wherein:

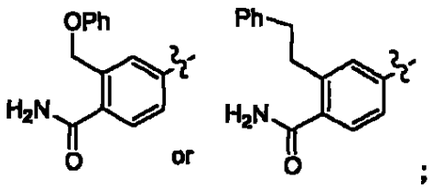
[00108] A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl; and

[00109] R^{10} is H.

[00110] In a ninth aspect, the present invention includes compounds of Formula (II), within the scope of the eighth aspect wherein:

[00111] A is 4-CH_2NH_2-cyclohexyl, 4-CO_2Me-cyclohexyl, 4-$CONH_2$-cyclohexyl, 4-$NHCO_2$(*t*-Bu)-cyclohexyl, 4-$NHCO_2$Bn-cyclohexyl, phenyl, 4-Me-phenyl, 3-OMe-phenyl, 4-CH_2NH_2-phenyl, 3-$CONH_2$-phenyl, 4-$CONH_2$-phenyl, 3-amidino-phenyl, 4-amidino-phenyl, 2-F-4-Me-phenyl, 2-Bn-4-CH_2NH_2-phenyl, 4-SO_2NH_2-phenyl, 2-F-5-OMe-phenyl, 2-F-4-Cl-phenyl, 2-F-4-CH_2NH_2-phenyl, 2-F-4-$CONH_2$-phenyl, 2-Cl-4-$CONH_2$-phenyl, 2-Et-4-CH_2NH_2-phenyl, 2-NHEt-4-CH_2NH_2-phenyl, 2-OMe-4-$CONH_2$-phenyl, 3-OMe-4-$CONH_2$-phenyl, 1,2,3,4-tetrahydronaphth-2-yl, 3-Cl-thien-2-yl, indol-5-yl, indol-5-yl, indazol-5-yl, indazol-6-yl, 3-NH_2-indazol-6-yl, 3-NH_2-indazol-5-yl, 1-Me-3-NH_2-indazol-6-yl, 3-NH_2-benzisoxazol-6-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 2-COPh-1,2,3,4-tetrahydroisoquinolin-3-yl, 2-CO_2Bn-1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-1-on-6-yl, 2H-isoquinolin-1-on-6-yl, isoquinolin-6-yl, 1-NH_2-isoquinolin-6-yl, 1-NH_2-3-Me-isoquinolin-6-yl, 1-NH_2-5,6,7,8-tetrahydroisoquinolin-6-yl,

4-NH_2-quinazolin-7-yl, 3H-quinazolin-4-on-7-yl,

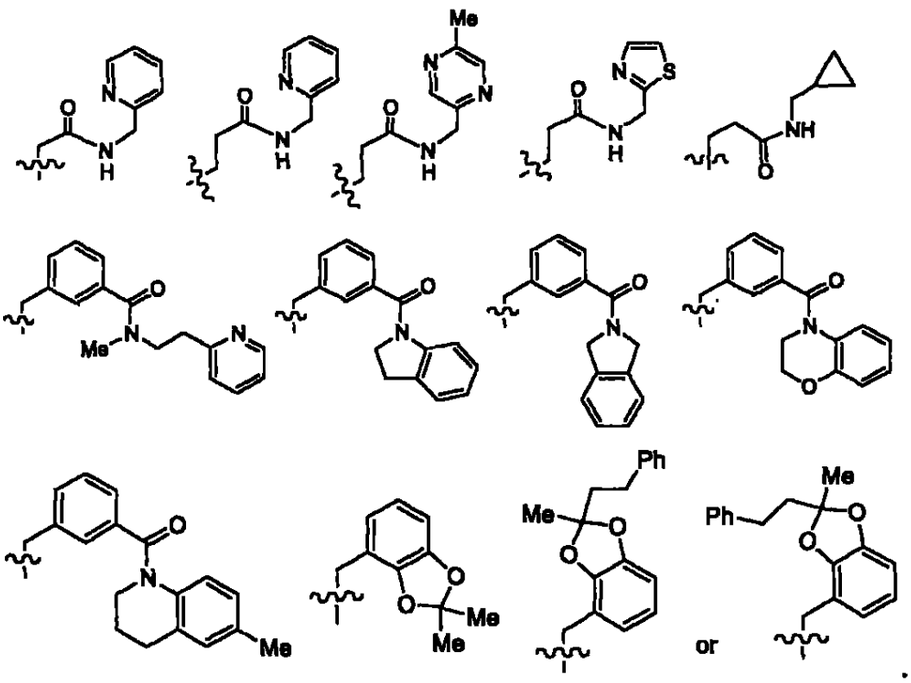


;

[00112] R^4 is H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, phenyl, 3-F-4-CN-phenyl, or 3-NH_2-6-indazolyl; and

[00113] R^{11} is Me, neopentyl, cyclohexylmethyl, -$CH_2CH_2CONHBn$, -$CH_2CH_2CONH(CH_2CH_2Ph)$, -$CH_2CH_2CON(Me)Bn$, benzyl, phenethyl, 2-Me-benzyl, 3-Me-benzyl, 4-Me-benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl, 2-Cl-benzyl, 3-Cl-benzyl, 4-Cl-benzyl, 2-Br-benzyl, 3-Br-benzyl, 4-Br-benzyl, 3-CF_3-benzyl, 4-CF_3-benzyl, 2-NH_2-benzyl, 3-NH_2-benzyl, 2-NO_2-benzyl, 3-NO_2-benzyl, 4-NO_2-benzyl, 3-OMe-benzyl, 4-OMe-benzyl, 3-OCF_2H-benzyl, 2-OCF_3-benzyl, 3-OCF_3-benzyl, 2-OPh-benzyl, 3-OPh-benzyl, 2-OBn-benzyl, 3-OBn-benzyl, 4-OBn-benzyl, 4-COPh-benzyl, 3-CO_2H-benzyl, 3-CO_2Me-benzyl, 3-NHAc-benzyl, 2-NHCOPh-benzyl, 2-NHCOBn-benzyl, 3-NHCOBn-benzyl, 3-N(Me)COPh-benzyl, 3-(-$NHCOCH_2CH_2Ph$)-benzyl, 2-$NHSO_2Ph$-benzyl, 3-$NHSO_2Ph$-benzyl, 3-[$SO_2N(Me)Ph$]-benzyl, 3-[$N(Me)SO_2Ph$]-benzyl, 3-[CONH(*i*-Bu)]-benzyl, 3-[CONH(*t*-Bu)]-benzyl, 3-[CONH(isopentyl)]-benzyl, 3-[CONH(2-Me-Ph)]-benzyl, 3-[CONH(3-Me-Ph)]-benzyl, 3-[CONH(4-Me-Ph)]-benzyl, 3-[CONH(4-F-Ph)]-benzyl, 3-[CONH(1-naphthyl)]-benzyl, 3-(CONHBn)-benzyl, 3-[CONH(4-Cl-Bn)]-benzyl, 3-[CONH(4-OMe-Bn)]-benzyl, 3-[$CONHCH_2CH_2Ph$]-benzyl, 3-[$CONHCH_2CH_2$(4-OMe-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(2-Cl-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(3-Cl-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(4-Cl-Ph)]-benzyl, 3-[$CONH(CH_2)_3Ph$]-benzyl, 3-[$CONMe_2$]-benzyl, 3-[CON(Me)(Et)]-benzyl, 3-[CON(Me)(*i*-Pr)]-benzyl, 3-[CON(Me)(*i*-Bu)]-benzyl, 3-[CON(Me)Ph]-benzyl, 3-[CON(Me)(3-Me-Ph)]-benzyl, 3-[CON(Me)(4-Me-Ph)]-benzyl, 3-[CON(Me)Bn]-benzyl, 3-[CON(Me)(3-Cl-Bn)]-benzyl, 3-[CON(Me)(4-Cl-Bn)]-benzyl, 3-[$CON(Me)(CH_2CH_2Ph)$]-benzyl,

3-[CON(Et)Ph]-benzyl, 3-[CO(1-piperidino)]-benzyl, 3-[CO(4-Ph-1-piperidino)]-benzyl, 3-[CO(1,2,3,4-tetrahydroisoquinolino)]-benzyl, 2-Ph-benzyl, 3-Ph-benzyl, 4-Ph-benzyl, 3-phenethyl-benzyl, -CH_2OBn, -CH_2SBn, 1-naphthylmethyl, 2-naphthylmethyl, thiazol-4-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, 1-Bn-imidazol-4-ylmethyl, benzothiazol-2-ylmethyl,



[00114] In a tenth aspect, the present invention includes compounds of Formula (II), within the scope of the eighth aspect wherein:

[00115] A is 4-CH_2NH_2-cyclohexyl, 4-$NHCO_2$(*t*-Bu)-cyclohexyl, 4-$NHCO_2$Bn-cyclohexyl, or 1-NH_2-5,6,7,8-tetrahydroisoquinolin-6-yl;

[00116] L is –C(O)NH- or NHC(O)-;

[00117] R^3 is indazol-5-yl, indazol-6-yl, 3-NH_2-indazol-5-yl, 3-OH-indazol-5-yl, 3-NH_2-indazol-6-yl, 3-NH_2-4-F-indazol-6-yl, 3-NH_2-5-F-indazol-6-yl, 3-NH_2-7-F-indazol-6-yl, or 4-NH_2-quinazolin-7-yl;

[00118] R^4 is H, Me, F, Br, Cl, or CF_3; and

[00119] R^{11} is benzyl substituted with 0-2 R^{11b}.

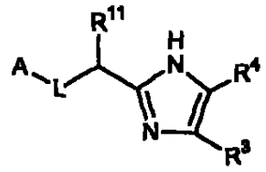
[00120] In an eleventh aspect, the present invention includes compounds of Formula (II), within the scope of the tenth aspect wherein:

[00121] A is 4-CH_2NH_2-cyclohexyl;

[00122] L is –C(O)NH-; and

[00123] R^3 is 3-NH_2-indazol-6-yl or 4-NH_2-quinazolin-7-yl.

[00124] In a twelfth aspect, the present invention includes a compound of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect wherein:

[00125] A is substituted with 0-2 R^1 and 0-1 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

[00126] L is -C(O)NR^{10}- or -NR^{10}C(O)-;

[00127] R^3 is -$(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00128] R^4 is H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et,

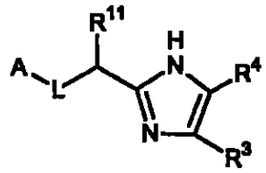
-$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b}; and

[00129] R^{11} is benzyl substituted with 0-2 R^{11b}.

[00130] In another aspect, the present invention includes a compound of Formula (II), within the scope of the twelfth aspect wherein:

[00131] R^3 is -$(CH_2)_r$-9- to 10-membered bicyclic heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a}.

[00132] In a thirteenth aspect, the present invention includes a compound of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect wherein:

[00133] A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

[00134] L is -$C(O)NR^{10}$- or -$NR^{10}C(O)$-;

[00135] R^3 is -$(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, -$(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d};

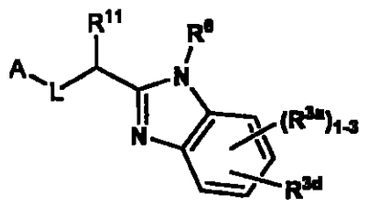
[00136] R^4 is, independently at each occurrence, H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, phenyl, 3-F-4-CN-phenyl, or 3-NH_2-6-indazolyl; and

[00137] R^{11} is benzyl substituted with 0-2 R^{11b}.

[00138] In another aspect, the present invention includes a compound of Formula (II), within the scope of the thirteenth aspect wherein:

[00139] R^3 is -$(CH_2)_r$-phenyl substituted with 0-3 R^{3a}.

[00140] In a fourteenth aspect, the present invention includes a compound of Formula (III):



(III)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect wherein:

[00141] R^{3a} is, independently at each occurrence, =O, F, Cl, Br, Me, CN, OH, NH_2, OMe, O(*t*-Bu), OBn, CF_3, CO_2H, CO_2Me, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, -NHCOMe, -$CONH_2$, -CH_2CONH_2, -CONHMe, -$CONMe_2$, -$C(=NH)NH_2$, -NR^7R^8, -SO_2Me, -SO_2NH_2, Ph, or 2-oxo-piperidin-1-yl;

[00142] R^{3d} is H or C_{1-4} alkyl;

[00143] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, -$(CH_2)_r$-phenyl substituted with 0-2 R^d, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

[00144] R^{11} is C_{1-4} haloalkyl, -$(CH_2)_r$-$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{11a}, C_{2-6} alkenyl substituted with 0-2 R^{11a}, C_{2-6} alkynyl substituted with 0-2 R^{11a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or -$(CH_2)_r$-5-10

membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

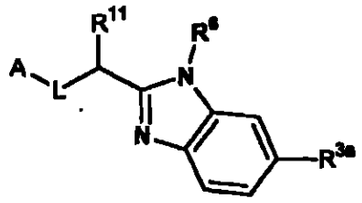
[00145] In a fifteenth aspect, the present invention includes compounds of Formula (III), within the scope of the fourteenth aspect wherein:

[00146] R^1 is, independently at each occurrence, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, or $-CH_2CH_2NH_2$;

[00147] R^{10} is H, Me, benzyl, or phenethyl; and

[00148] R^{11} is Me, $-(CH_2)_r$-phenyl substituted with 0-1 R^{11b}, or $-(CH_2)_r$-5-10 membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^{11b}.

[00149] In a sixteenth aspect, the present invention includes a compound of Formula (IV):



(IV)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect wherein:

[00150] A is cyclohexyl substituted with 1 R^1, phenyl substituted with 1 R^1, pyridyl substituted with 1 R^1, naphthyl substituted with 1 R^1, benzisoxazole substituted with 1 R^1, or isoquinolinyl substituted with 0-1 R^1;

[00151] L is $-C(O)NH-$, $-C(O)NMe-$, $-C(O)N(benzyl)-$, $-C(O)N(phenethyl)-$, $-NHC(O)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, or $-NHC(O)CH_2-$;

[00152] R^1 is, independently at each occurrence, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, or $-CH_2NH_2$;

[00153] R^{3a} is F, Cl, Br, Me, CN, OMe, CF_3, CO_2H, CO_2Me, CO_2Et,

$-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, $CONH_2$, -CONHMe, $-CON(Me)2$, $-CH_2CONH_2$, or $-C(=NH)NH_2$;

[00154] R^6 is H;

[00155] R^{10} is H, Me, benzyl, or phenethyl; and

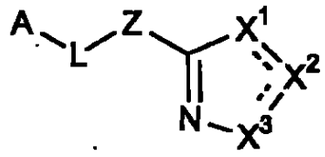
[00156] R^{11} is Me, $-(CH_2)_r$-phenyl substituted with 0-1 R^{11b}, or $-(CH_2)_r$-5-10 membered heteroaryl substituted with 0-1 R^{11b} and selected from thiazolyl, imidazolyl, pyridyl, and benzothiazolyl.

[00157] In a seventeenth aspect, the present invention includes compounds of Formula (IV), within the scope of the sixteenth aspect wherein:

[00158] A is $4\text{-}CH_2NH_2$-cyclohexyl or 4-amidino-phenyl; and

[00159] R^{3a} is, independently at each occurrence, CO_2H, CO_2Me, $-CH_2CO_2H$, $-CH_2CO_2Et$, $-CONH_2$, or $-CH_2CONH_2$.

[00160] In an eighteenth aspect, the present invention provides, *inter alia*, a compound of Formula (V):

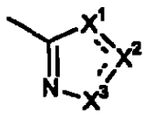
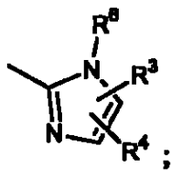


(V)

or its stereoisomers, tautomers, a pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein:

[00161] A is C_{3-10} carbocycle substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 12-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2; provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

[00162] X^1, X^2, and X^3 are independently CR^3, CR^4, CR^4R^5, O, $S(O)_p$, N, NR^3, NR^6, or C(O); provided that no S-S, S-O, or O-O bond is present in the ring;

[00163] provided that  is other than  ;

[00164] Z is $-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-(CH_2)-$, $-NR^{13}-$, or $-NR^{13}CH_2-$;

[00165] L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^{7}-$, $-NR^{7}CH_2-$, $-CH_2CH_2NR^{7}-$, $-NR^{7}CH_2CH_2$, $-CH_2NR^{7}CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, or $-C(O)CH_2-$;

[00166] R^1 is, independently at each occurrence, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7C(O)OR^a$, $-CH_2NH_2$, $-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl)$_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(C_{1-3}$ alkyl), $-CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $-CH(C_{1-4}$ alkyl)NH_2, $-C(C_{1-4}$ alkyl)$_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-cyclopropyl, or C_{1-6} alkyl substituted with 0-1 R^{1a};

[00167] R^{1a} is H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p-C_{1-4}$ alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

[00168] R^2 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$,

C_{1-6} alkyl substituted with 0-2 R^{2a}, C_{2-6} alkenyl substituted with 0-2 R^{2a}, C_{2-6} alkynyl substituted with 0-2 R^{2a}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{2b}, or $-(CH_2)_r$–5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{2b};

[00169] R^{2a} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[00170] R^{2b} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

[00171] alternately, when R^1 and R^2 groups are substituted on adjacent ring atoms, they can be taken together with the ring atoms to which they are attached to form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said carbocycle or heterocycle is substituted with 0-2 R^{2b};

[00172] R^3 is, independently at each occurrence, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$–5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00173] R^{3a} is, independently at each occurrence, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$,

$-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-C(O)-C_{1-4}$ alkyl, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, C_{1-6} alkyl substituted by R^{3d}, C_{2-6} alkenyl substituted by R^{3d}, C_{2-6} alkynyl substituted by R^{3d}, C_{3-6} cycloalkyl substituted by 0-1 R^{3d}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r-$5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00174] alternately, when two R^{3a} groups are located on adjacent atoms, they can be taken together with the atoms to which they are attached to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[00175] R^{3b} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r-$5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00176] R^{3c} is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r-$5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00177] R^{3d} is, independently at each occurrence, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$,

$-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_pR^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, C_{2-6} alkynyl substituted with 0-2 R^e, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00178] R^4 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{4b}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00179] R^{4a} is, independently at each occurrence, H, F, =O, C_{1-6} alkyl, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[00180] R^{4b} is, independently at each occurrence, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[00181] alternately, R^3 and R^4 groups when located on adjacent atoms, can be taken together to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[00182] R^5 is, independently at each occurrence, H, F, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$,

$-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{5a}, C_{2-6} alkenyl substituted with 0-2 R^{5a}, C_{2-6} alkynyl substituted with 0-2 R^{5a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{5b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{5b};

[00183] R^{5a} is, independently at each occurrence, H, =O, OR^a, SR^a, F, Cl, Br, I, CF_3, OCF_3, CN, NO_2, $-NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[00184] R^{5b} is, independently at each occurrence, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[00185] R^6 is, independently at each occurrence, H, C_{1-6} alkyl, C_{1-4} haloalkyl, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, $-S(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

[00186] R^7 is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n$-C_{3-10} carbocycle, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O$-(C_{1-4} alkyl)$OC(O)$-(C_{1-4} alkyl), or $-C(O)O$-(C_{1-4} alkyl)$OC(O)$-(C_{6-10} aryl); wherein said alkyl, carbocycle, heteroaryl, and aryl are optionally substituted with 0-2 R^f;

[00187] R^8 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_r$-phenyl, or $-(CH_2)_n$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said alkyl, phenyl and heterocycle are optionally substituted with 0-2 R^f;

[00188] alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2

additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[00189] R^{8a} is, independently at each occurrence, H, OH, C_{1-6} alkyl, C_{1-4} alkoxy, (C_{6-10} aryl)-C_{1-4} alkoxy, -$(CH_2)_n$-phenyl, -$(CH_2)_n$-(5-10 membered heteroaryl), -$C(O)R^c$, -$C(O)_2R^c$, -C(O)O-(C_{1-4} alkyl)OC(O)-(C_{1-4} alkyl), or -C(O)O-(C_{1-4} alkyl)OC(O)-(C_{6-10} aryl); wherein said phenyl, aryl, and heteroaryl is optionally substituted with 0-2 R^f;

[00190] R^9 is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl; wherein said alkyl and phenyl are optionally substituted with 0-2 R^f;

[00191] R^{9a} is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl;

[00192] alternatively, R^8 and R^9, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[00193] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, C_{2-6} alkenyl substituted with 0-3 R^{10a}, C_{2-6} alkynyl substituted with 0-3 R^{10a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00194] R^{10a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, SR^a, F, CF_3, CN, NO_2, -$C(O)OR^a$, -NR^7R^8, -$C(O)NR^7R^8$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8SO_2R^c$-, -$S(O)R^c$, or -$S(O)_2R^c$;

[00195] R^{11} is C_{1-4} haloalkyl, -$(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, -$(CR^{14}R^{15})_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or

-$(CR^{14}R^{15})_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b};

[00196] R^{11a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, CF_3, SR^a, F, CN, NO_2, NR^7R^8, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^c$, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^d;

[00197] R^{11b} is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00198] alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R&;

[00199] R^{12} is, independently at each occurrence, H, F, or C_{1-4} alkyl;

[00200] R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n$-phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, $-C(O)OR^c$, $-CONR^8R^c$, $-OCONR^8R^c$, $-S(O)_2R^c$, $-C(O)O-(C_{1-4}$ alkyl)$-OC(O)-(C_{1-4}$ alkyl), or $-C(O)O-(C_{1-4}$ alkyl)$-OC(O)-(C_{6-10}$ aryl); wherein the said alkyl, phenyl, heteroaryl, aryl are optionally substituted with 0-2 R^f;

[00201] R^{14} and R^{15} are, independently at each occurrence, H, F, or C_{1-4} alkyl;

[00202] alternately, R^{14} combines with R^{15} to form =O;

[00203] R^a is, independently at each occurrence, H, CF_3, C_{1-6} alkyl, $-(CH_2)_r-C_{3-7}$ cycloalkyl, $-(CH_2)_r-C_{6-10}$ aryl, or $-(CH_2)_r$-5- to 10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said cycloalkyl, aryl and heteroaryl groups are optionally substituted with 0-2 R^f;

[00204] R^b is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00205] R^c is, independently at each occurrence, CF_3, C_{1-6} alkyl substituted with 0-2 R^f, C_{3-6} cycloalkyl substituted with 0-2 R^f, C_{6-10} aryl, 5- to 10-membered heteroaryl, (C_{6-10} aryl)-C_{1-4} alkyl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl, wherein said aryl and heteroaryl groups are optionally substituted with 0-3 R^f;

[00206] R^d is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, or C_{2-6} alkynyl substituted with 0-2 R^e;

[00207] R^e is, independently at each occurrence, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

[00208] R^f is, independently at each occurrence, H, =O, -$(CH_2)_r$-ORg, F, Cl, Br, I, CN, NO_2, -$NR^{9a}R^{9a}$, -C(O)Rg, -C(O)ORg, -NR^{9a}C(O)Rg, -C(O)$NR^{9a}R^{9a}$, -$SO_2NR^{9a}R^{9a}$, -$NR^{9a}SO_2NR^{9a}R^{9a}$, -$NR^{9a}SO_2$-C_{1-4} alkyl, -$NR^{9a}SO_2CF_3$, -$NR^{9a}SO_2$-phenyl, -$S(O)_2CF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, -$(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or -$(CH_2)_n$-phenyl;

[00209] Rg is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl;

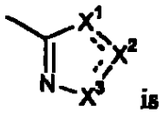
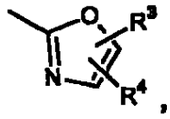
[00210] n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

[00211] p, at each occurrence, is selected from 0, 1, and 2;

[00212] r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

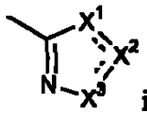
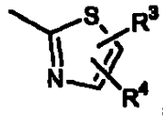
[00213] s, at each occurrence, is selected from 1, 2, 3, and 4;

[00214] provided that:

[00215] (a). when group  is  ,

[00216] i. and when L is –NHC(O)-, R^{14} does not combine with R^{15} to form =O;

[00217] ii. and when L is –C(O)NH- and A is phenyl, R^1 is not –NHC(O)H;

[00218] (b). when group  is  ,

[00219] i. and when L is –NHC(O)- and R^3 combines with R^4 to form a phenyl ring fused with the thiazole, the phenyl ring is substituted with at least one R^{3a};

[00220] ii. and when L is –C(O)NH- and A is phenyl, R^1 is not –NHC(O)H; and

[00221] (c). A is not a substituted or unsubstituted oxazolinone, thiophene, oxadiazole, or furan.

[00222] In a nineteenth aspect, the present invention includes compounds of Formula (V), within the scope of the eighteenth aspect wherein:

[00223] A is C_{3-8} cycloalkyl substituted with 0-1 R^1 and 0-3 R^2, C_{4-8} cycloalkenyl substituted with 0-1 R^1 and 0-3 R^2, phenyl substituted with 0-1 R^1 and 0-3 R^2, naphthyl substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2; provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

[00224] Z is $-C(R^{11})(R^{12})-$;

[00225] L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, or $-NR^{10}C(O)CH_2-$;

[00226] R^3 is, independently at each occurrence, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-C_{3-8} cycloalkyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00227] R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00228] R^6 is, independently at each occurrence, H, C_{1-6} alkyl, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

[00229] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, $-(CH_2)_r$-phenyl substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered

heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d; and

[00230] R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

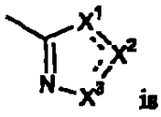
[00231] In a twentieth aspect, the present invention includes compounds of Formula (V), within the scope of the eighteenth aspect wherein:

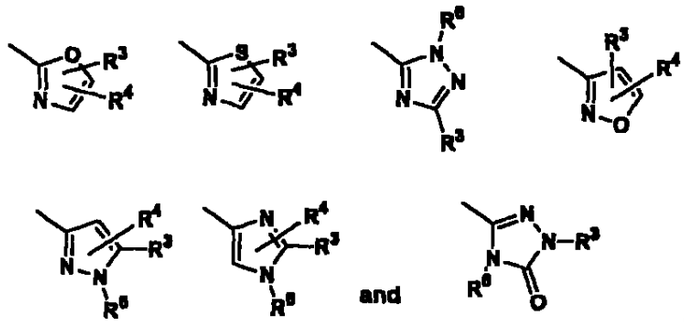
[00232] A is C_{5-6} cycloalkyl substituted with 0-1 R^1 and 0-2 R^2, C_{5-6} cycloalkenyl substituted with 0-1 R^1 and 0-2 R^2,, phenyl substituted with 0-1 R^1 and 0-3 R^2, naphthyl substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2; provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

[00233] R^3 is, independently at each occurrence, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d}; and

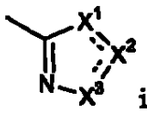
[00234] R^6 is, independently at each occurrence, H or C_{1-6} alkyl.

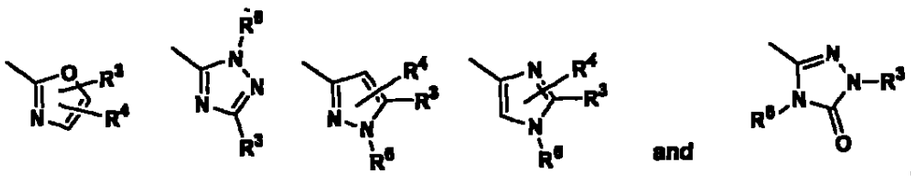
[00235] In a twenty first aspect, the present invention includes compounds of Formula (V), within the scope of the eighteenth aspect wherein:

[00236] the group  is selected from:



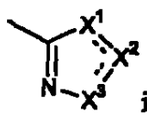
[00237] In a twenty second aspect, the present invention includes compounds of Formula (V), within the scope of the eighteenth aspect wherein:

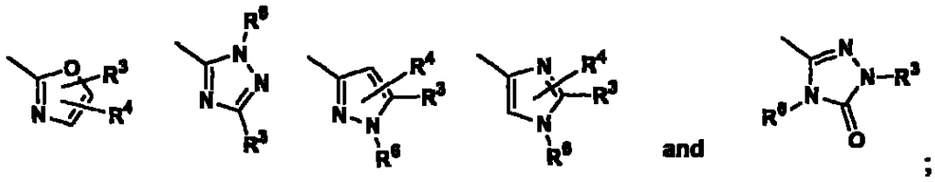
[00238] the group  is selected from:



[00239] In a twenty third aspect, the present invention includes compounds of Formula (V), within the scope of the eighteenth aspect wherein.

[00240] A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

[00241] the group  is selected from:



and ;

[00242] Z is –CH(R^{12})-;

[00243] L is -C(O)NR^{10}-, -NR^{10}C(O)-, -CH_2C(O)NR^{10}-, -CH_2NR^{10}C(O)-, -C(O)N$R^{10}$$CH_2$-, or -N$R^{10}$C(O)$CH_2$-;

[00244] R^3 is, independently at each occurrence, -$(CH_2)_r$C(O)NR^8R^9, -$(CH_2)_r$C(O)N$R^8$$(CH_2)_s$$CO_2R^{3b}$, -$(CH_2)_r$$CO_2R^{3b}$, -$(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, -$(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, -$(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d} or -$(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^{3a} and 0-1 R^{3d};

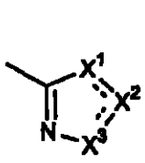
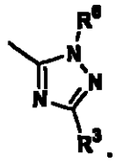
[00245] R^4 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CN, NO_2, -C(O)R^a, -C(O)OR^a, -NR^7R^8, -C(O)NR^8R^9, -NR^7C(O)R^b, -$S(O)_p$NR^8R^9, -N$R^8$$S(O)_p$$R^c$, -S(O)$R^c$, -$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^{4b};

[00246] R^6 is H, C_{1-6} alkyl, or -$(CH_2)_r$-phenyl substituted with 0-3 R^d;

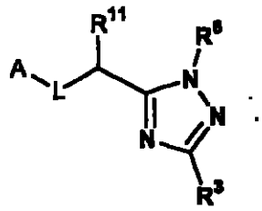
[00247] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, -$(CH_2)_r$-phenyl substituted with 0-2 R^d, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

[00248] R^{12} is, independently at each occurrence, H, F, or Me.

[00249] In another aspect, the present invention includes compounds of Formula (V), within the scope of the twenty second aspect wherein.

[00250] the group  is  .

[00251] In a twenty fourth aspect, the present invention includes a compound of Formula (VI):



(VI)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the eighteenth aspect wherein:

[00252] R^3 is $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_sC(O)NR^8(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{3a}, $-(CH_2)_r$-indanyl substituted with 0-2 R^{3a}, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00253] R^6 is, independently at each occurrence, H, C_{1-6} alkyl, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

[00254] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d; and

[00255] R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

[00256] In a twenty fifth aspect, the present invention includes compounds of Formula (VI), within the scope of the twenty fourth aspect wherein:

[00257] R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, $-NHEt$, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

[00258] R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)_r$-phenyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, naphthyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, indanyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, or a $-(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a} and 0-1 R^{3d};

[00259] R^6 is H;

[00260] R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, or

[00255] R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

[00256] In a twenty fifth aspect, the present invention includes compounds of Formula (VI), within the scope of the twenty fourth aspect wherein:

[00257] R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, $-NHEt$, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

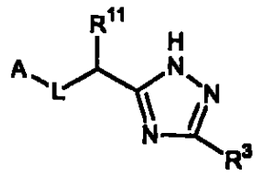
[00258] R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)_r$-phenyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, naphthyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, indanyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, or a $-(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a} and 0-1 R^{3d};

[00259] R^6 is H;

[00260] R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, or $-CH_2CH_2CONHCH_2CH_2Ph$; and

[00261] R^{11} is C_{1-6} alkyl, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{11b}.

[00262] In a twenty sixth aspect, the present invention includes a compound of Formula (VII):



(VII)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the eighteenth aspect wherein:

[00263] A is substituted with 0-2 R^1 and 0-1 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

[00264] L is -C(O)NH- or -NHC(O)-;

[00265] R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

[00266] R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, -C(O)NHMe, -C(O)NHBn, phenyl substituted with 0-2 R^{3a}, naphthyl substituted with 0-2 R^{3a}, indanyl substituted with 0-2 R^{3a}, or a 5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a};

[00267] R^4 is H, F, Cl, Br, CF_3, CO_2H, CO_2Me, CO_2Et, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{4b};

[00268] R^{11} is C_{1-6} alkyl, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r-C_{3-7}$ cycloalkyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or $-(CH_2)_r$-5- to 10-membered heteroaryl substituted with 0-2 R^{11b} and selected from thiazolyl, oxazolyl, triazolyl, tetrazolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl; and

[00269] R^{11b} is, independently at each occurrence, H, F, Cl, Br, CF_3, OMe, OEt, O(*i*-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, C_1-C_4-alkyl, Ph, or Bn;

[00270] alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R8.

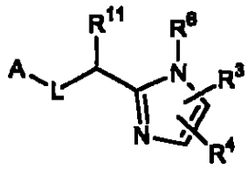
[00271] In a twenty seventh aspect, the present invention includes compounds of Formula (V), within the scope of the twenty sixth aspect wherein:

[00272] A is 4-CH_2NH_2-cyclohexyl or 4-amidino-phenyl; and

[00273] R^3 is phenyl, 3-CN-phenyl, 4-CN-phenyl, 3-Br-phenyl, 4-Br-phenyl, 3-OMe-phenyl, 4-OMe-phenyl, 3-CF_3-phenyl, 4-CF_3-phenyl, 3-CO_2H-phenyl, 4-CO_2H-phenyl, 4-CO_2Me-phenyl, 4-CH_2CO_2H-phenyl, 4-CH_2CO_2Me-phenyl, 3-$CONH_2$-phenyl, 4-$CONH_2$-phenyl, 4-CONHMe-phenyl, 4-$CON(Me)_2$-phenyl, 4-CH_2CONH_2-phenyl, 4-amidino-phenyl, or 2,4-diF-phenyl.

[00274] In a twenty eighth aspect, the present invention includes, *inter alia*, a method for treating a thromboembolic or an inflammatory disorder, comprising:

administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I):



(I)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein:

[00275] A is C_{3-10} carbocycle substituted with 0-3 R^1 and 0-1 R^2, or a 5- to 12-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^1 and 0-1 R^2;

[00276] L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, or $-C(O)CH_2-$;

[00277] R^1 is, independently at each occurrence, $-NH_2$, $-NH(C_1-C_3$ alkyl), $-N(C_1-C_3$ alkyl)$_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7CO_2R^a$, $-CH_2NH_2$, $-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl)$_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(C_1-C_3$ alkyl), $-CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $-CH(C_{1-4}$ alkyl)NH_2, $-C(C_{1-4}$ alkyl)$_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-cyclopropyl, or C_{1-6} alkyl substituted with 0-1 R^{1a};

[00278] R^{1a} is H, -C(=NR^{8a})NR^7R^8, -NHC(=NR^{8a})NR^7R^8, -NR^8CH(=NR^{8a}), -NR^7R^8, -C(O)NR^8R^9, F, OCF_3, CF_3, OR^a, SR^a, CN, -$NR^9SO_2NR^8R^9$, -$NR^8SO_2R^c$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, or -$(CF_2)_rCF_3$;

[00279] R^2 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -NR^7R^8, -C(O)NR^7R^8, -NR^7C(O)R^b, -$S(O)_2NR^8R^9$, -$NR^8S(O)_2R^c$, -S(O)R^c, -$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{2a}, C_{2-6} alkenyl substituted with 0-2 R^{2a}, C_{2-6} alkynyl substituted with 0-2 R^{2a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{2b}, or -$(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{2b};

[00280] R^{2a} is, independently at each occurrence, H, F, Cl, Br, I, =O, =NR^8, CN, OCF_3, CF_3, OR^a, SR^a, -NR^7R^8, -C(O)NR^8R^9, -NR^7C(O)R^b, -$S(O)_pNR^8R^9$, -$NR^8SO_2R^c$, -S(O)R^c, or -$S(O)_2R^c$;

[00281] R^{2b} is, independently at each occurrence, H, F, Cl, Br, I, =O, =NR^8, CN, NO_2, CF_3, OR^a, SR^a, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -NR^7R^8, -C(O)NR^7R^8, -NR^7C(O)R^b, -$S(O)_2NR^8R^9$, -$S(O)_2R^c$, -$NR^8SO_2NR^8R^9$, -$NR^8SO_2R^c$, -$(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[00282] alternately, when R^1 and R^2 groups are substituted on adjacent ring atoms, they can be taken together with the ring atoms to which they are attached to form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said carbocycle or heterocycle is substituted with 0-2 R^{2b};

[00283] R^3 is F, Cl, Br, -$(CH_2)_r$C(O)NR^8R^9, -$(CH_2)_r$C(O)$NR^8(CH_2)_sCO_2R^{3b}$, -$(CH_2)_rCO_2R^{3b}$, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$-5- to 10-membered heterocycle

comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00284] R^{3a} is, independently at each occurrence, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, SR^{3b}, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, C_{1-4} alkyl-C(O)-, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, C_{1-6} alkyl substituted by R^{3d}, C_{2-6} alkenyl substituted by R^{3d}, C_{2-6} alkynyl substituted by R^{3d}, C_{3-6} cycloalkyl substituted by 0-1 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r$–5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00285] alternately, when two R^{3a} groups are located on adjacent atoms, they can be taken together with the atoms to which they are attached to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[00286] R^{3b} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r$–5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00287] R^{3c} is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2

R^{3d}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{3d}, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00288] R^{3d} is, independently at each occurrence, H, =O, -$(CH_2)_r$$OR^a$, F, Cl, Br, CN, NO_2, -$(CH_2)_r$$NR^7R^8$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -$NR^7C(O)R^b$, -$C(O)NR^8R^9$, -$SO_2NR^8R^9$, -$NR^8SO_2NR^8R^9$, -$NR^8SO_2R^c$, -$S(O)_pR^c$, -$(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, C_{2-6} alkynyl substituted with 0-2 R^e, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00289] R^4 is H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_pR^c$, -$S(O)R^c$, -$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{4b}, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00290] R^{4a} is, independently at each occurrence, H, F, =O, C_{1-6} alkyl, OR^a, SR^a, CF_3, CN, NO_2, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$,-$S(O)_pNR^8R^9$, -$NR^8S(O)_2R^c$, -$S(O)R^c$, or -$S(O)_2R^c$;

[00291] R^{4b} is, independently at each occurrence, H, =O, =NR^8, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, -SO_2R^c, -NR^7R^8, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[00292] alternately, R^3 and R^4 groups when located on adjacent atoms, can be taken together to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-

membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[00293] R^6 is, independently at each occurrence, H, C_{1-6} alkyl, C_{1-4} haloalkyl, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, $-S(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

[00294] R^7 is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n$-C_{3-10} carbocycle, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O$-(C_{1-4} alkyl)OC(O)-(C_{1-4} alkyl), or $-C(O)O$-(C_{1-4} alkyl)OC(O)-(C_{6-10} aryl); wherein said alkyl, carbocycle, heteroaryl, and aryl are optionally substituted with 0-2 R^f;

[00295] R^8 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl, or $-(CH_2)_n$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said alkyl, phenyl and heterocycle are optionally substituted with 0-2 R^f;

[00296] alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[00297] R^{8a} is, independently at each occurrence, H, OH, C_{1-6} alkyl, C_{1-4} alkoxy, (C_{6-10} aryl)-C_{1-4} alkoxy, $-(CH_2)_n$-phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O$-(C_{1-4} alkyl)OC(O)-(C_{1-4} alkyl), or $-C(O)O$-(C_{1-4} alkyl)OC(O)-(C_{6-10} aryl); wherein said phenyl, aryl, and heteroaryl is optionally substituted with 0-2 R^f;

[00298] R^9 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_r$ -phenyl; wherein said alkyl and phenyl are optionally substituted with 0-2 R^f;

[00299] R^{9a} is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

[00300] alternatively, R^8 and R^9, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[00301] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, C_{2-6} alkenyl substituted with 0-3 R^{10a}, C_{2-6} alkynyl substituted with 0-3 R^{10a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00302] R^{10a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$-, $-S(O)R^c$, or $-S(O)_2R^c$;

[00303] R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CR^{14}R^{15})_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CR^{14}R^{15})_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b};

[00304] R^{11a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, CF_3, SR^a, F, CN, NO_2, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^c$, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^d;

[00305] R^{11b} is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$,

$-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$–5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00306] alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R^g;

[00307] R^{14} and R^{15} are, independently at each occurrence, H, F, or C_{1-4} alkyl;

[00308] alternately, R^{14} combines with R^{15} to form =O;

[00309] R^a is, independently at each occurrence, H, CF_3, C_{1-6} alkyl, $-(CH_2)_r$–C_{3-7} cycloalkyl, $-(CH_2)_r$–C_{6-10} aryl, or $-(CH_2)_r$–5- to 10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said cycloalkyl, aryl and heterocycle groups are optionally substituted with 0-2 R^f;

[00310] R^b is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$–5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00311] R^c is, independently at each occurrence, CF_3, C_{1-6} alkyl substituted with 0-2 R^f, C_{3-6} cycloalkyl substituted with 0-2 R^f, C_{6-10} aryl, 5- to 10-membered heteroaryl, (C_{6-10} aryl)-C_{1-4} alkyl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl, wherein said aryl and heteroaryl groups are optionally substituted with 0-3 R^f;

[00312] R^d is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$,

$-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, or C_{2-6} alkynyl substituted with 0-2 R^e;

[00313] R^e is, independently at each occurrence, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

[00314] R^f is, independently at each occurrence, H, =O, $-(CH_2)_r$-ORg, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, -C(O)Rg, -C(O)ORg, $-NR^{9a}C(O)$Rg, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-C_{1-4} alkyl, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-(CH_2)_n$-phenyl;

[00315] Rg is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

[00316] n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

[00317] p, at each occurrence, is selected from 0, 1, and 2;

[00318] r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

[00319] s, at each occurrence, is selected from 1, 2, 3, and 4.

[00320] In a twenty ninth aspect, the present invention provides a method for treating a thromboembolic or an inflamunatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I), within the scope of the twenty eighth aspect wherein:

[00321] L is $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, $-CH_2CONR^{10}$-, or $-NR^{10}COCH_2$-;

[00322] R^3 is $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d},

-$(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, -$(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00323] R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00324] R^6 is H, C_{1-6} alkyl, $-CH_2OR^a$, or -$(CH_2)_r$-phenyl substituted with 0-3 R^d;

[00325] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, -$(CH_2)_r$-phenyl substituted with 0-2 R^d, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

[00326] R^{11} is C_{1-4} haloalkyl, -$(CH_2)_r$-$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{11a}, C_{2-6} alkenyl substituted with 0-2 R^{11a}, C_{2-6} alkynyl substituted with 0-2 R^{11a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

[00327] In a thirtieth aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I), within the scope of the twenty eighth aspect wherein:

[00328] R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$,

-C(=NH)NH_2, -C(O)NH_2, -CH_2NH_2, -$CH_2CH_2NH_2$, -CH_2NHCO_2Bn, -CH_2NHCO_2(*t*-Bu), -CH(Me)NH_2, -C(Me)$_2NH_2$, -NHEt, -$NHCO_2$(*t*-Bu), -$NHCO_2Bn$, -SO_2NH_2, OR^a, or -CH_2OR^{1a};

[00329] R^3 is -CO_2H, -CO_2Me, -C(O)$NHCH_2CO_2H$, -C(O)$NHCH_2CO_2Et$, -C(O)NH_2, -C(O)NHMe, -C(O)NHBn, -$(CH_2)_r$-phenyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, naphthyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, indanyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a} and 0-1 R^{3d};

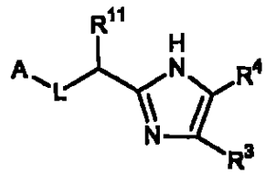
[00330] R^4 is H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, -$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00331] R^6 is H, Me, benzyl, or phenethyl;

[00332] R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, -$CH_2CH_2CO_2H$, -$CH_2CH_2CO_2Me$, -$CH_2CH_2CO_2Et$, -$CH_2CH_2CONH_2$, or -$CH_2CH_2CONHCH_2CH_2Ph$; and

[00333] R^{11} is C_{1-6} alkyl, -$CH_2CONR^8R^9$, -$CH_2CH_2CONR^8R^9$, -CH_2OBn, -CH_2SBn, -$(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{11b}.

[00334] In a thirty first aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the twenty eighth aspect wherein:

[00335] A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

[00336] L is -C(O)NH-, -C(O)NMe-, -C(O)N(benzyl)-, -C(O)N(phenethyl)-, -NHC(O)-, $-S(O)_2NH-$, $-CH_2C(O)NH-$, $-C(O)NHCH_2-$, $-CH_2NHC(O)-$ or $-NHC(O)CH_2-$;

[00337] R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

[00338] R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, -C(O)NHMe, -C(O)NHBn, phenyl substituted with 0-2 R^{3a}, naphthyl substituted with 0-2 R^{3a}, indanyl substituted with 0-2 R^{3a}, or a 5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a};

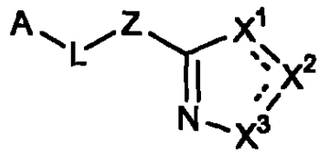
[00339] R^4 is H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{4b};

[00340] R^{11} is C_{1-6} alkyl, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r-C_{3-7}$ cycloalkyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or $-(CH_2)_r$-5- to 10-membered heteroaryl substituted with 0-2 R^{11b} and selected from thiazolyl, oxazolyl, triazolyl, tetrazolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl; and

[00341] R^{11b} is, independently at each occurrence, H, F, Cl, Br, CF_3, OMe, OEt, O(*i*-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, C_1-C_4-alkyl, Ph, or Bn;

[00342] alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R§.

[00343] In a thirty second aspect, the present invention provides, *inter alia*, a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (V):



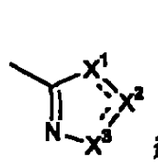
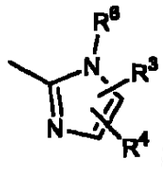
(V)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein:

[00344] A is C_{3-10} carbocycle substituted with 0-3 R^1 and 0-1 R^2, or a 5- to 12-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected

from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^1 and 0-1 R^2;

[00345] X^1, X^2, and X^3 are independently CR^3, CR^4, CR^4R^5, O, $S(O)_p$, N, NR^3, NR^6, or C(O); provided that no S-S, S-O, or O-O bond is present in the ring;

[00346] provided that  is other than  ;

[00347] Z is $-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-(CH_2)-$, $-NR^{13}-$, or $-NR^{13}CH_2-$;

[00348] L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, or $-C(O)CH_2-$;

[00349] R^1 is, independently at each occurrence, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7C(O)OR^a$, $-CH_2NH_2$, $-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl$)_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(C_{1-3}$ alkyl), $-CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $-CH(C_{1-4}$ alkyl$)NH_2$, $-C(C_{1-4}$ alkyl$)_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-cyclopropyl, or C_{1-6} alkyl substituted with 0-1 R^{1a};

[00350] R^{1a} is H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p-C_{1-4}$ alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

[00351] R^2 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{2a}, C_{2-6} alkenyl substituted with 0-2 R^{2a}, C_{2-6} alkynyl substituted with 0-2 R^{2a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{2b}, or $-(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{2b};

[00352] R^{2a} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[00353] R^{2b} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, CF_3, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

[00354] alternately, when R^1 and R^2 groups are substituted on adjacent ring atoms, they can be taken together with the ring atoms to which they are attached to form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said carbocycle or heterocycle is substituted with 0-2 R^{2b};

[00355] R^3 is, independently at each occurrence, F, Cl, Br, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00356] R^{3a} is, independently at each occurrence, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, SR^{3b}, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, C_{1-4} alkyl-C(O)-, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, C_{1-6} alkyl substituted by R^{3d}, C_{2-6} alkenyl substituted by R^{3d}, C_{2-6} alkynyl substituted by R^{3d}, C_{3-6} cycloalkyl substituted by 0-1 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00357] alternately, when two R^{3a} groups are located on adjacent atoms, they can be taken together with the atoms to which they are attached to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[00358] R^{3b} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00359] R^{3c} is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r$-5- to 10-

membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

[00360] R^{3d} is, independently at each occurrence, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_pR^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, C_{2-6} alkynyl substituted with 0-2 R^e, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00361] R^4 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{4b}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00362] R^{4a} is, independently at each occurrence, H, F, =O, C_{1-6} alkyl, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[00363] R^{4b} is, independently at each occurrence, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[00364] alternately, R^3 and R^4 groups when located on adjacent atoms, can be taken together to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-

membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

[00365] R^5 is, independently at each occurrence, H, F, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{5a}, C_{2-6} alkenyl substituted with 0-2 R^{5a}, C_{2-6} alkynyl substituted with 0-2 R^{5a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{5b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{5b};

[00366] R^{5a} is, independently at each occurrence, H, =O, OR^a, SR^a, F, Cl, Br, I, CF_3, OCF_3, CN, NO_2, $-NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

[00367] R^{5b} is, independently at each occurrence, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

[00368] R^6 is, independently at each occurrence, H, C_{1-6} alkyl, C_{1-4} haloalkyl, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, $-S(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^{3d};

[00369] R^7 is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n$-C_{3-10} carbocycle, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O$-(C_{1-4} alkyl)$OC(O)$-(C_{1-4} alkyl), or $-C(O)O$-(C_{1-4} alkyl)$OC(O)$-(C_{6-10} aryl); wherein said alkyl, carbocycle, heteroaryl, and aryl are optionally substituted with 0-2 R^f;

[00370] R^8 is, independently at each occurrence, H, C_{1-6} alkyl, or

-$(CH_2)_r$-phenyl, or -$(CH_2)_n$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said alkyl, phenyl and heterocycle are optionally substituted with 0-2 R^f;

[00371] alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[00372] R^{8a} is, independently at each occurrence, H, OH, C_{1-6} alkyl, C_{1-4} alkoxy, (C_{6-10} aryl)-C_{1-4} alkoxy, -$(CH_2)_n$-phenyl, -$(CH_2)_n$-(5-10 membered heteroaryl), -$C(O)R^c$, -$C(O)_2R^c$, -C(O)O-(C_{1-4} alkyl)OC(O)-(C_{1-4} alkyl), or -C(O)O-(C_{1-4} alkyl)OC(O)-(C_{6-10} aryl); wherein said phenyl, aryl, and heteroaryl is optionally substituted with 0-2 R^f;

[00373] R^9 is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$ -phenyl; wherein said alkyl and phenyl are optionally substituted with 0-2 R^f;

[00374] R^{9a} is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl;

[00375] alternatively, R^8 and R^9, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

[00376] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, C_{2-6} alkenyl substituted with 0-3 R^{10a}, C_{2-6} alkynyl substituted with 0-3 R^{10a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00377] R^{10a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, SR^a, F, CF_3, CN, NO_2, -$C(O)OR^a$, -NR^7R^8, -$C(O)NR^7R^8$, -$NR^7C(O)R^b$,

$-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$-, $-S(O)R^c$, or $-S(O)_2R^c$;

[00378] R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CR^{14}R^{15})_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CR^{14}R^{15})_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b};

[00379] R^{11a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, CF_3, SR^a, F, CN, NO_2, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^c$, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^d;

[00380] R^{11b} is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00381] alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 Rg;

[00382] R^{12} is, independently at each occurrence, H, F, or C_{1-4} alkyl;

[00383] R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n$-phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, $-C(O)OR^c$,

-$CONR^8R^c$, -$OCONR^8R^c$, -$S(O)_2R^c$, -C(O)O-(C_{1-4} alkyl)-OC(O)-(C_{1-4} alkyl), or -C(O)O-(C_{1-4} alkyl)-OC(O)-(C_{6-10} aryl); wherein the said alkyl, phenyl, heteroaryl, aryl are optionally substituted with 0-2 R^f;

[00384] R^{14} and R^{15} are, independently at each occurrence, H, F, or C_{1-4} alkyl;

[00385] alternately, R^{14} combines with R^{15} to form =O;

[00386] R^a is, independently at each occurrence, H, CF_3, C_{1-6} alkyl, -$(CH_2)_r$-C_{3-7} cycloalkyl, -$(CH_2)_r$-C_{6-10} aryl, or -$(CH_2)_r$-5- to 10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said cycloalkyl, aryl and heteroaryl groups are optionally substituted with 0-2 R^f;

[00387] R^b is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or -$(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

[00388] R^c is, independently at each occurrence, CF_3, C_{1-6} alkyl substituted with 0-2 R^f, C_{3-6} cycloalkyl substituted with 0-2 R^f, C_{6-10} aryl, 5- to 10-membered heteroaryl, (C_{6-10} aryl)-C_{1-4} alkyl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl, wherein said aryl and heteroaryl groups are optionally substituted with 0-3 R^f;

[00389] R^d is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, -NR^7R^8, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -$NR^8C(O)R^a$, -$C(O)NR^7R^8$, -$SO_2NR^8R^9$, -$NR^8SO_2NR^8R^9$, -NR^8SO_2-C_{1-4} alkyl, -$NR^8SO_2CF_3$, -NR^8SO_2-phenyl, -$S(O)_2CF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, -$(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, or C_{2-6} alkynyl substituted with 0-2 R^e;

[00390] R^e is, independently at each occurrence, =O, OR^a, F, Cl, Br, I, CN, NO_2, -NR^8R^9, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -$NR^8C(O)R^a$, -$C(O)NR^7R^8$,

$-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

[00391] R^f is, independently at each occurrence, H, =O, $-(CH_2)_r-OR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-C_{1-4} alkyl, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-(CH_2)_n$-phenyl;

[00392] R^g is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

[00393] n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

[00394] p, at each occurrence, is selected from 0, 1, and 2;

[00395] r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

[00396] s, at each occurrence, is selected from 1, 2, 3, and 4.

[00397] In a thirty third aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (V), within the scope of the thirty second aspect wherein:

[00398] A is C_{3-8} cycloalkyl substituted with 0-1 R^1 and 0-3 R^2, C_{4-8} cycloalkenyl substituted with 0-1 R^1 and 0-3 R^2, phenyl substituted with 0-1 R^1 and 0-3 R^2, naphthyl substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2;

[00399] Z is $-C(R^{11})(R^{12})-$;

[00400] L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, or $-NR^{10}C(O)CH_2-$;

[00401] R^3 is, independently at each occurrence, F, Cl, Br,

$-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-C_{3-8} cycloalkyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d},or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

[00402] R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

[00403] R^6 is, independently at each occurrence, H, C_{1-6} alkyl $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

[00404] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d; and

[00405] R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

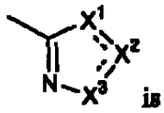
[00406] In a thirty fourth aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (V), within the scope of the thirty second aspect wherein:

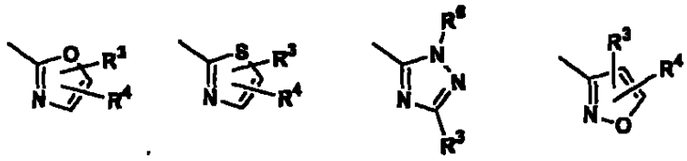
[00407] A is C_{5-6} cycloalkyl substituted with 0-1 R^1 and 0-2 R^2, C_{5-6} cycloalkenyl substituted with 0-1 R^1 and 0-2 R^2,, phenyl substituted with 0-1 R^1 and 0-3 R^2, naphthyl substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2;

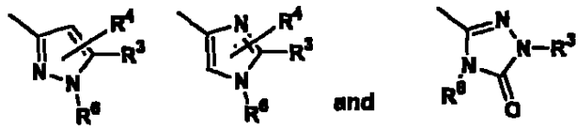
[00408] R^3 is, independently at each occurrence, F, Cl, Br, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d}; and

[00409] R^6 is, independently at each occurrence, H or C_{1-6} alkyl.

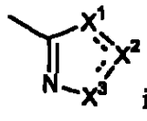
[00410] In a thirty fifth aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (V), within the scope of the thirty second aspect wherein:

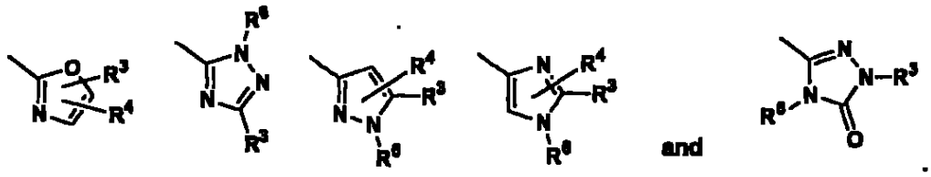
[00411] the group  is selected from:





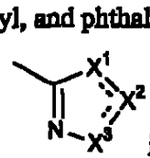
[00412] In a thirty sixth aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (V), within the scope of the thirty second aspect wherein:

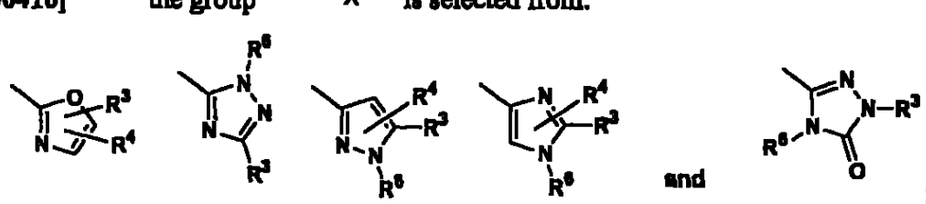
[00413] the group  is selected from:



[00414] In a thirty seventh aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (III), within the scope of the thirty second aspect wherein.

[00415] A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

[00416] the group  is selected from:

 ;

[00417] Z is $-CH(R^{12})-$;

[00418] L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, or $-NR^{10}C(O)CH_2-$;

[00419] R^3 is, independently at each occurrence, F, Cl, Br, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d} or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^{3a} and 0-1 R^{3d};

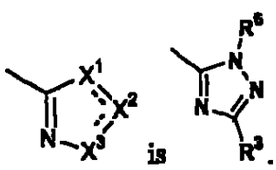
[00420] R^4 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^{4b};

[00421] R^6 is H, C_{1-6} alkyl, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

[00422] R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, $-(CH_2)_r$-phenyl substituted with 0-2 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

[00423] R^{12} is, independently at each occurrence, H, F, or Me.

[00424] In another aspect, the present invention provides a method for treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (III), within the scope of the twenty eighth aspect wherein.

[00425] the group  is .

[00426] In another aspect, L is -C(O)NR^{10}- or -NR^{10}C(O)-.

[00427] In another aspect, L is -C(O)NR^{10}-.

[00428] In another aspect, L is -NR^{10}C(O)-.

[00429] In another aspect, L is -C(O)NH- or -NHC(O)-.

[00430] In another aspect, L is -C(O)NH-.

[00431] In another aspect, L is -NHC(O)-.

[00432] In another aspect, the present invention provides a compound selected from the exemplified examples or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[00433] In another embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof.

[00434] In another embodiment, the present invention provides a novel process for making a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug form thereof.

[00435] In another embodiment, the present invention provides a novel intermediate for making a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug form thereof.

[00436] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from potassium channel openers, calcium channel blockers, sodium hydrogen exchanger inhibitors, antiarrhythmic agents, antiatherosclerotic agents, anticoagulants, antithrombotic agents, prothrombolytic agents, fibrinogen antagonists, diuretics,

antihypertensive agents, ATPase inhibitors, mineralocorticoid receptor antagonists, phospodiesterase inhibitors, antidiabetic agents, anti-inflammatory agents, antioxidants, angiogenesis modulators, antiosteoporosis agents, hormone replacement therapies, hormone receptor modulators, oral contraceptives, antiobesity agents, antidepressants, antianxiety agents, antipsychotic agents, antiproliferative agents, antitumor agents, antiulcer and gastroesophageal reflux disease agents, growth hormone agents and/or growth hormone secretagogues, thyroid mimetics, anti-infective agents, antiviral agents, antibacterial agents, antifungal agents, cholesterol/lipid lowering agents and lipid profile therapies, and agents that mimic ischemic preconditioning and/or myocardial stunning, or a combination thereof.

[00437] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from an anti-arrhythmic agent, an anti-hypertensive agent, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, a fibrinolytic agent, a calcium channel blocker, a cholesterol/lipid lowering agent, or a combination thereof.

[00438] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatroban, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, dipyridamol, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, ximelagatran, disulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase, or a combination thereof.

[00439] In a preferred embodiment, the present invention provides a pharmaceutical composition wherein the additional therapeutic agent is an antihypertensive agent selected from ACE inhibitors, AT-1 receptor antagonists, ET receptor antagonists, dual ET/AII receptor antagonists, and vasopepsidase inhibitors, an antiarrythmic agent selected from IKur inhibitors, or an antithrombotic agent selected from anticoagulants selected from thrombin inhibitors, other factor XIa inhibitors, other kallikrein inhibitors, factor VIIa inhibitors and factor Xa inhibitors,

and antiplatelet agents selected from GPIIb/IIIa blockers, $P2Y_1$ and $P2Y_{12}$ antagonists, thromboxane receptor antagonists, and aspirin, or a combination thereof.

[00440] In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent(s) are an anti-platelet agent or a combination thereof.

[00441] In a preferred embodiment, the present invention provides a pharmaceutical composition, wherein the additional therapeutic agent is the anti-platelet agent clopidogrel.

[00442] In another embodiment the present invention provides a method for modulation of the coagulation cascade and/or contact activation system comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof.

[00443] In another embodiment, the present invention provides a novel method for treating thromboembolic disorders comprising: administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof.

[00444] In another embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, and venous cerebrovascular thromboembolic disorders.

[00445] In another embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected unstable angina, an acute coronary syndrome, atrial fibrillation, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, and (f) other

procedures in which blood is exposed to an artificial surface that promotes thrombosis.

[00446] In another embodiment, the present invention provides a method for treating inflammatory disorders comprising: administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof.

[00447] In another embodiment, the present invention provides a method, wherein the inflammatory disorder is selected from the group consisting of sepsis, acute respiratory dystress syndrome, and systemic inflammatory response syndrome.

[00448] In another embodiment, the present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof in an amount effective to treat a thromboembolic disorder.

[00449] In another embodiment, the present invention provides a method of treating a patient in need of inflammatory disorder treatment, comprising: administering a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof in an amount effective to treat an inflammatory disorder.

[00450] In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof; and

(c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic and/or inflammatory disorder.

[00451] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

[00452] In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof; and

(c) a package insert stating that the pharmaceutical composition can be used in combination with a second therapeutic agent to treat a thromboembolic and/or inflammatory disorder.

[00453] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

[00454] In another embodiment, the present invention provides a novel method, comprising: administering a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof in an amount effective to treat a thromboembolic and/or inflammatory disorder.

[00455] In another embodiment, the present invention provides a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof, for use in therapy.

[00456] In another embodiment, the present invention also provides the use of a compound of the present invention or a stereoisomer, tautomer, a pharmaceutically acceptable salt, solvate or prodrug form thereof, for the manufacture of a medicament for the treatment of a thromboembolic and/or inflammatory disorder.

[00457] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in

conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DEFINITIONS

[00458] Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Accordingly, the present compounds can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated. All tautomers of shown or described compounds are also considered to be part of the present invention.

[00459] Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, or 800 grams per mole. Preferably, the molecular weight is less than about 800 grams per mole. More preferably, the molecular weight is less than about 750 grams per mole. Even more preferably, the molecular weight is less than about 700 grams per mole.

[00460] As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_1-C_{10} alkyl" or "C_{1-10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_{1-6} alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or substituted so that one or more of its hydrogens are replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl),

butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), and the like.

[00461] Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

[00462] "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

[00463] "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" refers to branched and straight-chained, having one or more halogen substituents. Example haloalkyl groups include, but are not limited to, CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2C_5, and the like.

[00464] The term "alkoxy" or "alkyloxy" refers to an –O-alkyl group. "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and t-butoxy, and the like. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S-, ethyl-S-, and the like.

[00465] "Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluorothoxy, and the like. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above

with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, pentafluoroethyl-S-, and the like.

[00466] The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like.

[00467] As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and indanyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00468] "Aryl" groups refer to monocyclic or polycyclic aromatic hydrocarbons, including, for example, phenyl, naphthyl, phenanthranyl, and the like. Aryl moieties are well known and described, for example, in *Hawley's Condensed Chemical Dictionary* (13 ed.), R.J. Lewis, ed., J. Wiley & Sons, Inc., New York (1997). Aryl groups can be substituted or unsubstituted.

[00469] As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7- membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, 13, or 14-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or fully unsaturated, and which consists of carbon atoms and 1, 2, 3 or 4

heteroatoms independently selected from N, O and S; and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

[00470] Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl,

thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[00471] Preferred 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl; octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

[00472] Preferred 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[00473] As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, benzodioxane, and the like. Heteroaryl groups can be substituted or unsubstituted. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$). It is to be noted that total number of S and O atoms in the aromatic

heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00474] The term "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

[00475] As referred to herein, the term "substituted" means that one or more hydrogen atoms is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (*e.g.*, carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (*i.e.*, within) of the ring.

[00476] When any variable (*e.g.*, R^{2a}, R^{2b}, etc.) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^{2b}, then said group may optionally be substituted with up to three R^{2b} groups and R^{2b} at each occurrence is selected independently from the definition of R^{2b}. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00477] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00478] When a dotted ring is used within a 5- to 8-membered ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

[00479] As used herein, the term "protecting group" for amines means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: (Fmoc); (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and t-butyl; and trialkylsilane types such as trimethylsilane.

[00480] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00481] The term "pharmaceutically acceptable salt" refers to acid or base salts of the compounds described herein. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as

amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference in its entirety. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[00482] In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. 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, at pp. 309-396, edited by K. 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, at pp. 113-191 (1991);

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, p. 1-38 (1992);

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

e) N. Kakeya, *et. al.*, *Chem Phar Bull.*, Vol. 32, p. 692 (1984).

[00483] Preparation of prodrugs is well known in the art and described in, for example, *Medicinal Chemistry: Principles and Practice*, ed. F. D. King, The Royal Society of Chemistry, Cambridge, UK, 1994, which is incorporated herein by reference in its entirety.

[00484] Radiolabelled compounds of the present invention, i.e., wherein one or more of the atoms described are replaced by a radioactive isotope of that atom (*e.g.*, C replaced by ^{13}C or by ^{14}C; and isotopes of hydrogen include tritium and deuterium), are also provided herein. Such compounds have a variety of potential uses, *e.g.*, as standards and reagents in determining the ability of a potential pharmaceutical to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors in vivo or in vitro.

[00485] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 98%, preferably 99%, compound of the present invention ("substantially pure"), which is then used or formulated as described herein. Such "substantially pure" compounds are also contemplated herein as part of the present invention.

[00486] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that compounds of the present invention do not contain a N-halo, $S(O)_2H$, or S(O)H group.

[00487] It should further be understood that solvates (*e.g.*, hydrates) of the compounds of the present invention are also with the scope of the present invention. Methods of solvation are generally known in the art.

[00488] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b)

inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

[00489] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit factor XIa and/or plasma kallikrein. "Therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit factor XIa and/or plasma kallikrein. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* 1984, *22*:27-55, occurs when the effect (in this case, inhibition of factor XIa and/or plasma kallikrein) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antithrombotic and/or anti-inflammatory effect, or some other beneficial effect of the combination compared with the individual components.

[00490] The present invention further includes compositions comprising one or more compounds of the present invention and a pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources

such as, for example, *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety.

SYNTHESIS

[00491] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

[00492] It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group(s) (PG) used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley-Interscience, 3rd Edition, 1999).

[00493] All references cited herein are hereby incorporated in their entirety herein by reference.

[00494] Imidazole compounds useful for the synthesis of the compounds of this invention may be synthesized according to the general method outlined in Scheme 1 (Con tour-Galcera *et al. Bioorg. Med. Chem. Lett.* 2001, *11*(5), 741-745). An appropriately protected or derivatized alpha amino acid [1; Y = R^{10}(PG)N- or Y = AC(O)N(R^{10})-] or malonic acid derivative [1; Y = alkyl-OC(O)-] is dissolved in an suitable solvent, such as ethanol/water (1:1), and treated with a base, such as cesium carbonate, to form the cesium salt. The salt is isolated and re-suspended in a suitable solvent, such as dimethyl formamide, and combined with an alpha-bromoketone 2 to form the keto ester 3. Alternatively, formation of keto ester 3 (X = aryl or heteroaryl) may be carried out in a single reaction vessel by forming the cesium salt of 1 in the same solvent (e.g., dimethyl formamide) used for the alkylation step.

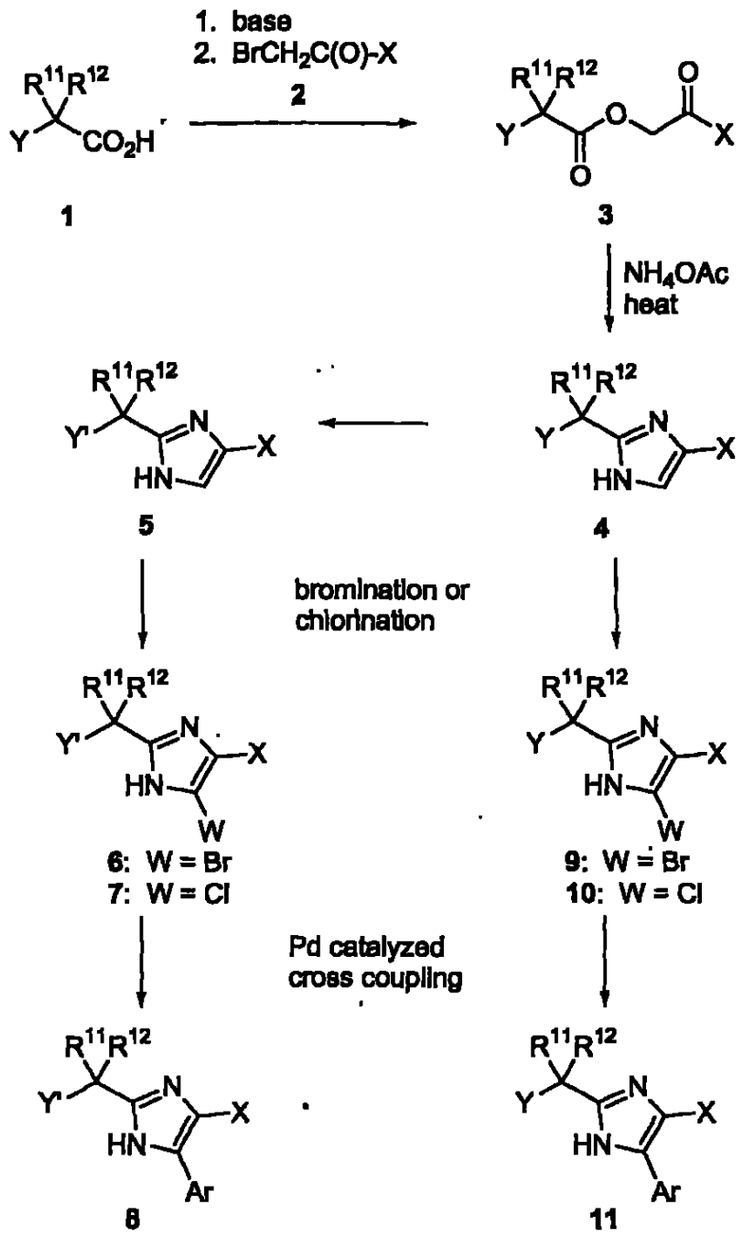
[00495] The imidazole having structure 4 is formed by heating the keto ester 3 to reflux in a suitable solvent, such as xylenes, in the presence of excess ammonium acetate using a Dean-Stark trap to remove water. Formation of the imidazole can also be carried out by combining the keto ester 3 and ammonium acetate in a suitable solvent, such as xylene or ethanol or a combination of solvents such as dimethylforamide and ethanol (1:1), using microwave heating. When Y = R^{10}(PG)N-, the protecting group on the amine is removed in preparation for acylation of the amine, which is outlined in Scheme 18. For example, when the protecting group is a BOC moiety, the amine is de-protected with strong acid, such as trifluoroacetic acid in suitable solvent, such as dichloromethane, to give compound 5, where Y' = R^{10}HN-. When Y = Alk-OCO-, the ester may be hydrolyzed by dissolving it in a suitable solvent such as methanol and treating the ester with a base such as aqueous sodium hydroxide to give 5 where Y = -CO_2H.

[00496] Further functional group incorporation on to the imidazole ring may be achieved by bromination of the C-5 carbon of the imidazole ring using, for example, bromine or N-bromosuccinimide, in a suitable solvent such as methylene chloride or chloroform to give compounds 6 and 9. Alternatively, the C-5 carbon may be

chlorinated with, for example, N-chlorosuccinimide, using a suitable solvent such as methylene chloride, acetonitrile or chloroform to give compounds **7** and **10**.

[00497] The brominated imidazoles **6** and **9** provide suitable functionality for futher elaboration using a wide variety of palladium catalyzed cross coupling procedures known to those skilled in the art such as described by Tsuji (*Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, John Wiley & Sons, Ltd., 2004). By way of example, application of a Suzuki coupling protocol using a modified method of Zhong *et al.* (*Org. Lett.* **2004**, *6*, 929-931) and Bellina *et al.* (*Synthesis* **2004**, *15*, 2419-2440), where the bromides **6** or **9** are combined with a boronic acid in the presence of a base, typically tribasic potassium phosphate or sodium carbonate, and a palladium catalyst, typically bis-(tri-t-butylphosphine) palladium (0), tris-(dibenzylidene-acetone) palladium (0), or tetrakis-(triphenylphosphine) palladium (0), in a suitable solvent, such as toluene or 1,4-dioxane heated to between 80 – 110 °C using conventional or microwave heating, provides structures **8** and **11**, where X = aryl or heteroaryl.

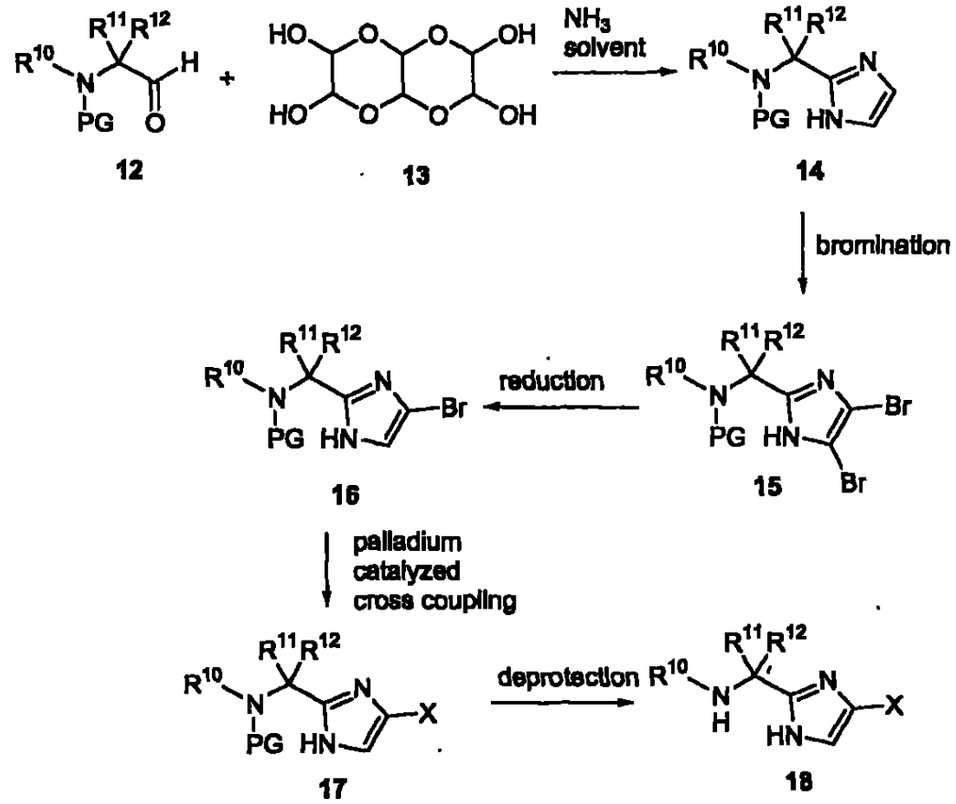
Scheme 1



[00498] An alternate synthesis of the imidazole core is shown in Scheme 2. A suitably protected beta amino aldehyde 12, glyoxal trimeric dihydrate 13 and ammonia are combined in a suitable solvent such as methanol and stirred together at room temperature. The resulting imidazole 14 is dissolved in a suitable solvent such

as chloroform and brominated using, for example, N-bromosuccinimide. Other brominating reagents may be employed, such as bromine, and other solvents suitable for bromination conditions, such as methylene chloride or carbon tetrachloride, may be used. The 4,5-dibromo imidazole 15 is treated with a reducing agent such as sodium hydrogen sulfite utilizing a biphasic solvent system consisting of, for example, 1,4-dioxane and water, and a phase transfer catalyst such as tetrabutylammonium hydrogen sulfate. The mono-bromide 16 thus produced may be combined with a suitably functionalized aryl boronic acid or heteroaryl boronic acid in a suitable solvent such as 1,4-dioxane or toluene, and treated at elevated temperature with a reagent combination consisting of, for example, palladium (I) tri-tert-butylphosphine bromide dimer and tribasic potassium phosphate according to a modified procedure of Zhong *et al.* and Bellini *et al.* referenced previously. Other reagent combinations that may be utilized for the Suzuki coupling procedure are palladium tris-(dibenzylidene-acetone) palladium (0), tri-(tert-butyl)-phosphonium tetra-fluoroborate, and tribasic potassium phosphate. The protecting group on the amine is removed in preparation for acylation of the amine, which is outlined in Scheme 17. For example, when the protecting group is a BOC moiety, the amine is de-protected with strong acid, such as trifluoroacetic acid, in suitable solvent, such as dichloromethane, to give amine 18 as the bis-TFA salt.

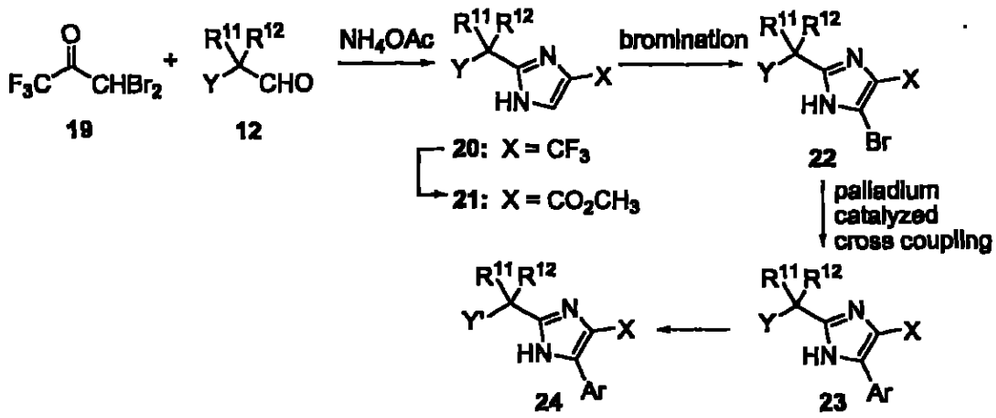
Scheme 2



12 13 14 15 16 17 18

[00499] Another alternative method for the synthesis of the imidazole ring is shown in Scheme 3. 3,3-Dibromo-1,1,1-trifluoropropan-2-one (19) is combined with ammonium acetate in a suitable solvent such as water and heated to 90 °, followed by the addition of a suitably protected aldehyde 12. The trifluoromethyl imidazole thus produced provides an intermediate for the synthesis of C-5 trifluoro methyl analogs illustrated by compound 24, where X = CF_3. Such compounds may be accessed by methods previously illustrated in Schemes 1 and 2. Alternatively, the trifluoromethyl moiety may be hydrolyzed under strongly basic conditions using, for example sodium methoxide, to provide the ortho ester which is hydrolyzed to the methyl ester 21, where X = $-CO_2CH_3$. This intermediate may be utilized using procedures already illustrated in Schemes 1 and 2 to access compounds such as 24, where X = $-CO_2CH_3$.

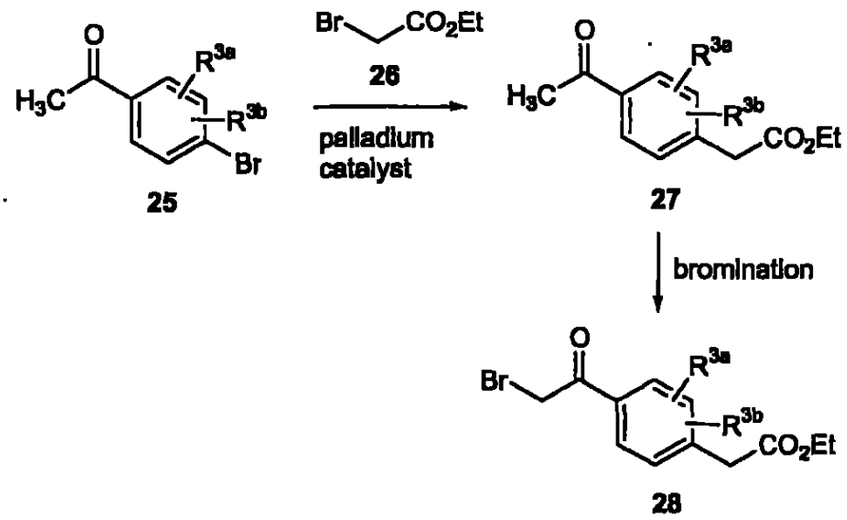
Scheme 3



[00500] Phenylalanine analogs bearing substituents on the phenyl ring not commercially available are readily accessed using methods known to those skilled in the art. For an authoritative review of methods for the synthesis of such analogs starting from glycine see Maruoka and Ooi (*Chem. Rev.* 2003, *103*, 3013-3028).

[00501] Certain 2-bromoacetophenone analogs that are not commercially available may be synthesized from commercially available starting materials. For example, ethyl 2-(4-(2-bromoacetyl)phenyl)acetate (27: $R^{3a} = R^{3b} = H$) can be prepared as shown in Scheme 4. 2,4'-dibromoacetophenone (25: $R^{3a} = R^{3b} = H$), and ethyl bromoacetate (26) are dissolved in a suitable solvent, such as tetrahydrofuran, and treated at elevated temperature with a combination of reagents, such as palladium (II) acetate, tris-(1-naphthyl) phosphine and tri-basic potassium phosphate according to the method of Gossen *et al.* (*Chem. Commun.* 2001, 669-670). The intermediate, ethyl 2-(4-acetylphenyl)acetate (27) is brominated by dissolving in a suitable solvent such as chloroform and treating with a brominating reagent such as bromine to give ethyl 2-(4-(2-bromoacetyl)phenyl)acetate (28). This reaction sequence may also be employed to prepare the other regioisomers and analogs of 28 containing functional groups compatible with the reaction sequence described.

Scheme 4

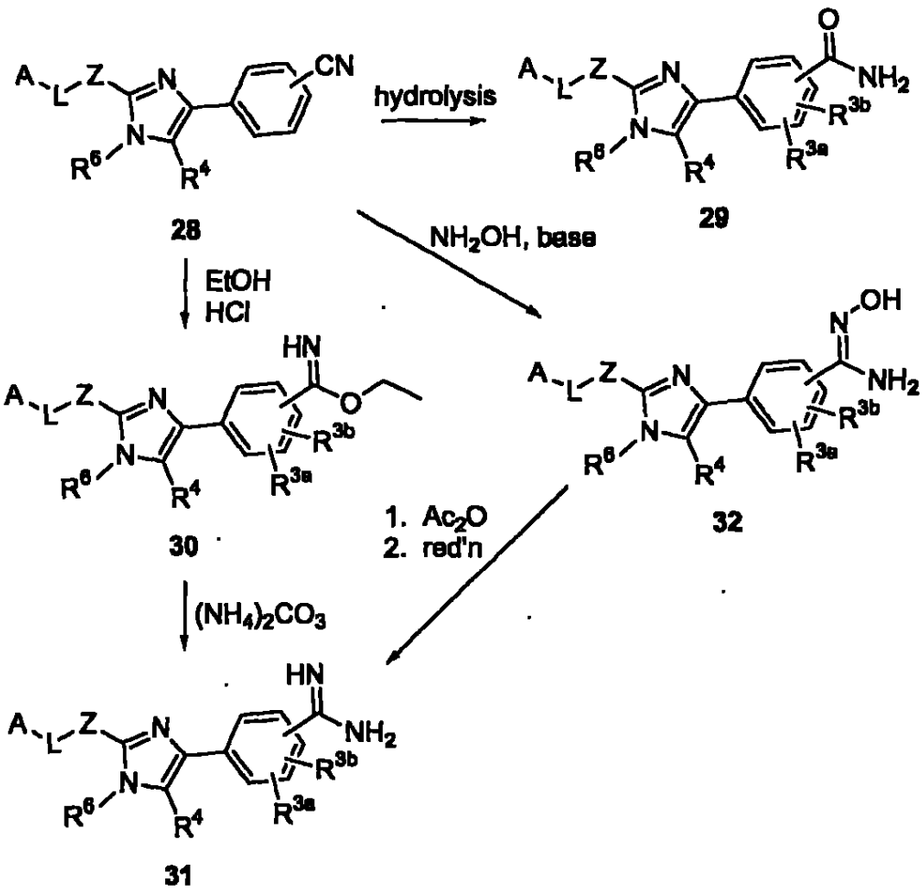


[00502] Certain functional groups present in the final structures must, by virtue of incompatibility with the formation of the imidazole shown in Schemes 1-3, be incorporated into the structure after the imidazole ring has been formed. Examples of such functional groups include, but are not limited to, carbamoyl, aminoindazolyl, aminobenzisoxazolyl, and aminoquinazolinoyl (see Schemes 5 and 6).

[00503] The carbamoyl group, illustrated in structure 29 in Scheme 5, may be incorporated into the final structure by hydrolysis of a nitrile using, for example, potassium carbonate, hydrogen peroxide, and DMSO as solvent, according to the method of Katritzky et al. (*Synthesis* 1989, 12, 949-50). When the nitrile is located para to the imidazole ring, magnesium oxide must be added to the reaction mixture. The amidine group, illustrated in structure 31, may be incorporated into the final structure via Pinner reaction followed by ammonolysis. Alternatively, the nitrile 28 may be combined with hydroxylamine hydrochloride in the presence of a base, such as triethylamine, to give the amidoxime 32, which after acetylation with acetic anhydride is reduced by a variety of methods including, but not limited by, catalytic hydrogenation using, for example, palladium on carbon and hydrogen (Judkins et al. Syn. *Comm.* 1996, *26*, 4351-4367), or by using an active metal such as zinc. By way of illustration, the precursor nitrile group shown in structure 28 in Scheme 5 may be incorporated on to the intermediate structure(s) by using, in separate reactions, 4-(2-

bromo-acetyl)-benzonitrile, 3-(2-bromo-acetyl)-benzonitrile, or 2-(2-bromo-acetyl)-benzonitrile for the reagent described as $BrCH_2C(O)X$ in Scheme 1.

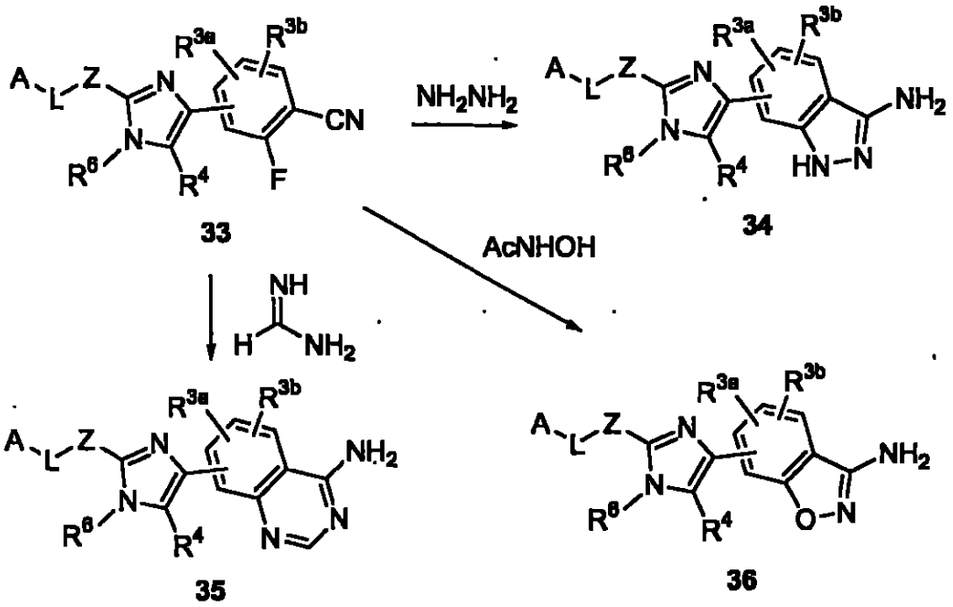
Scheme 5



[00504] The aminoindazole, aminobenzisoxazole and aminoquinazoline functional groups may be incorporated into the final structure using a common intermediate containing a phenyl ring bearing an ortho fluoro nitrile as illustrated in structure 33 (Scheme 6). The amino-indazole functional group (34) is produced, for example, by heating 33 with hydrazine monohydrate in a suitable solvent, such as n-butanol. Heating may be done conventially or via microwave irradiation, and the temperature required for conversion of the ortho fluoro nitrile to the aminoindazole depends upon the regioisomeric relationship between the ortho fluoro nitrile and the imidazole ring. Typically, temperatures of 160 °C are required for formation of the

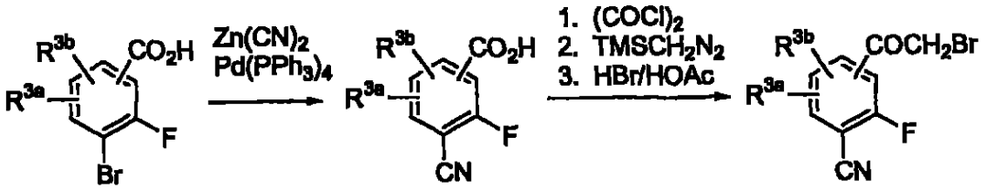
amino-indazole when the nitrile is located para to the imidazole ring. The aminoquinazoline (35) is produced by combining the *ortho*-fluoronitrile (33) with formamidine acetate, or other suitable salt forms, in a suitable solvent such as dimethyl acetamide or dimethyl formamide, and heating to approximately 140 °C. Conversion of the *ortho*-fluoronitrile to the aminobenzisoxazole (36) may be accomplished by combining the fluoro nitrile 33 with acetoxyhydroxamic acid in the presence of a base such as potassium carbonate.

Scheme 6



[00505] A general synthesis of alpha bromoketones containing an ortho fluoro nitrile is illustrated in Scheme 7. A suitably substituted bromo-fluoro-benzoic acid (37) is converted to the corresponding nitrile 38 using, for example, zinc cyanide and palladium (0) tetrakis-(triphenylphosphine) in a suitable solvent, such as dimethyl formamide, and heating to 90 °C. The nitrile 38 thus produced is treated sequentially with oxalyl chloride in a suitable solvent, such as dichloromethane, containing a few drops of DMF, then treated with trimethylsilyldiazomethane in a suitable solvent or solvent combination, such as acetonitrile and hexane. The intermediate diazoketone is isolated and treated with hydrobromic acid and acetic acid to provide the alpha bromoketone 39.

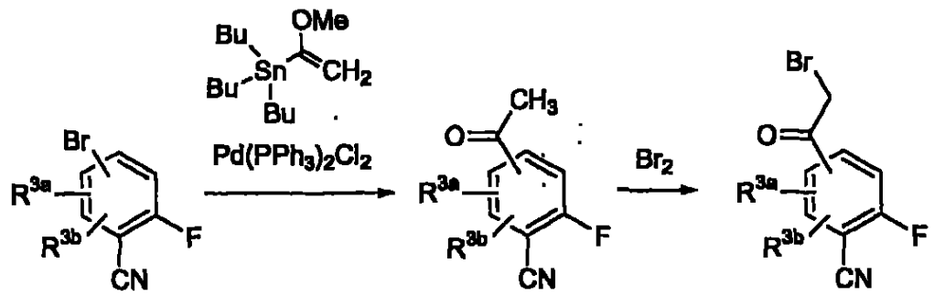
Scheme 7



37 38 39

[00506] Alternatively, the bromoketone 39 may be synthesized from a suitably substituted ortho fluoro nitrile containing a bromide (40 Scheme 8) by treatment sequentially with tributyl-(1-methoxyvinyl) stannane and a palladium catalyst, such as bis-(triphenylphosphine)-dichloro-palladium (II), in a suitable solvent, such as toluene, and heated to reflux, followed by aqueous hydrochloric acid, typically at 5% (w/v) concentration. The resulting methyl ketone 41 is combined with bromine in a suitable solvent, such as chloroform or methylene chloride, to produce the bromoketone 39. Alternate synthetic routes to 39 other than those illustrated in Schemes 7 and 8 may be envisioned by one skilled in the art depending on the regioisomers commercially available for possible combinations of R^{3a} and R^{3b} contained on the carbocylic ring.

Scheme 8

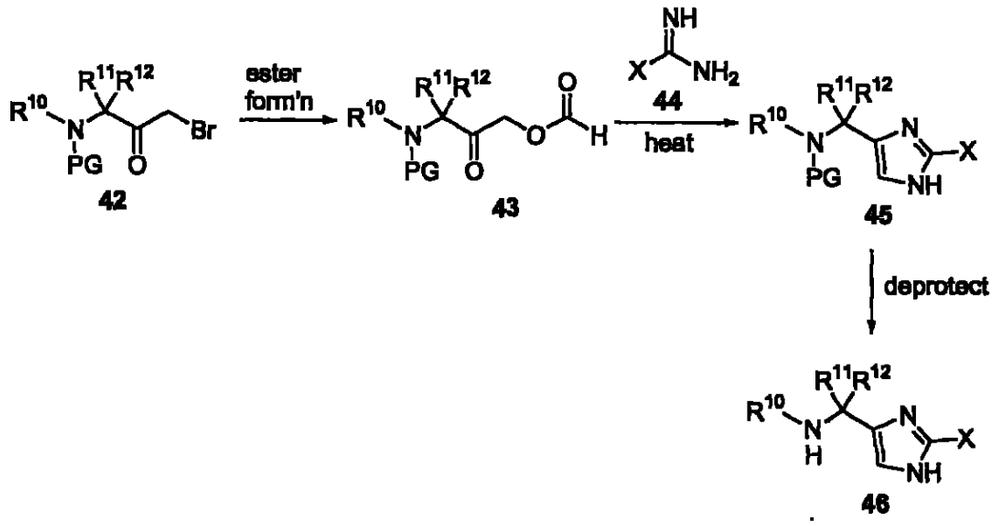


40 41 39

[00507] A different sequence of chemical transformations provides for the synthesis of a second regioisomer of the imidazoles useful in the preparation of compounds of this invention as shown in Scheme 9. An alpha-bromoketone 42 containing suitable substitution is combined with sodium formate in a suitable solvent, such as ethanol, and heated to reflux. The keto ester 43 thus formed is

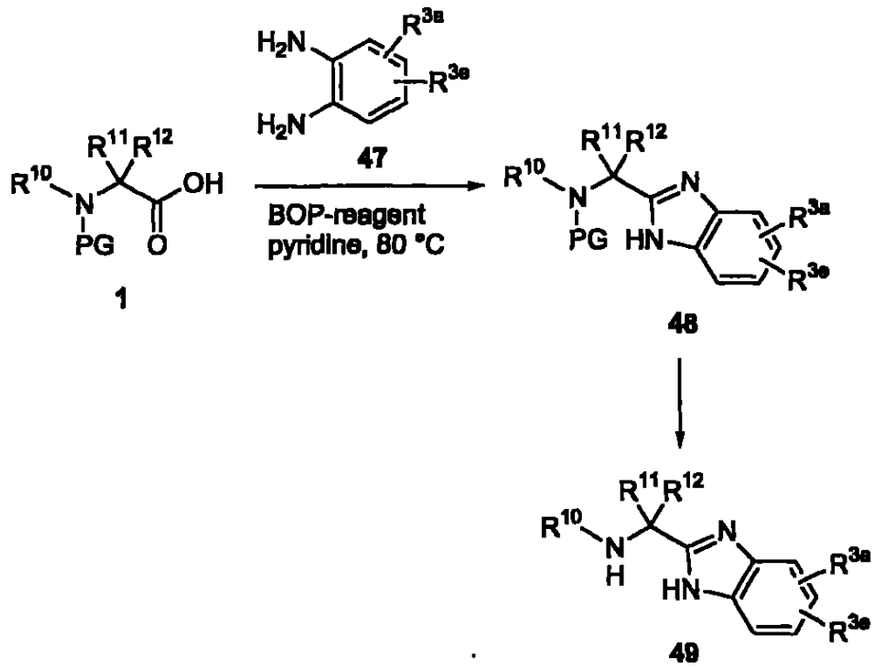
dissolved in a solvent, for example ethanol, and combined with a suitably substituted amidine 44 (X = aryl or heteroaryl) in the presence of a base, for example sodium bicarbonate. The imidazole 45 thus formed has the opposite regio-configuration compared to the imidazoles illustrated in Schemes 1-3. Removal of the amine protecting group, PG, in preparation for acylation of the amino group is carried out as described previously to give the amino imidazole 46.

Scheme 9



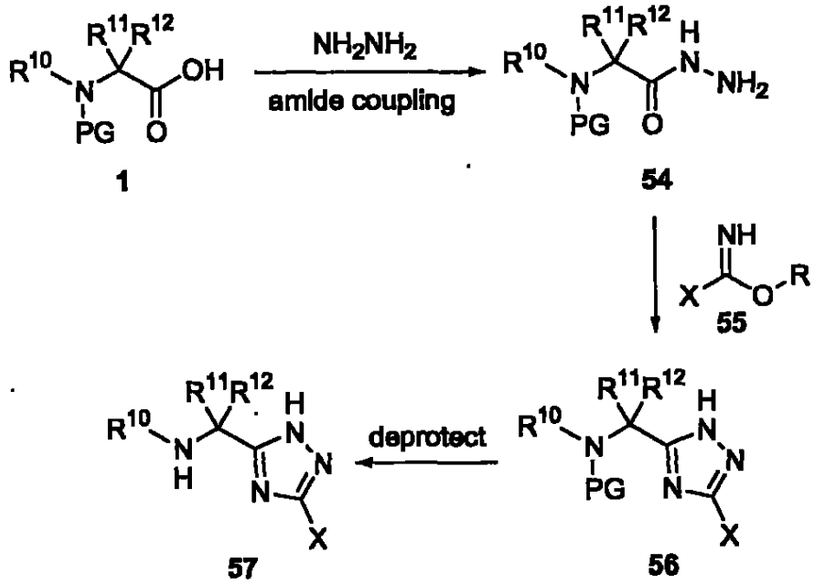
[00508] Benzimidazole compounds useful for preparing compounds of this invention can be synthesized according to the general procedure shown in Scheme 10. A suitably protected amino acid and a suitably substituted phenyl diamine 22 are dissolved in a solvent, for example pyridine, and treated with an amide bond forming reagent, such as BOP-reagent. The reaction mixture is heated to 80 °C to effect ring closure to the benzimidazole 23. The protecting group on the amine is removed as before in preparation for acylation of the amine, as outlined below in Scheme 17.

Scheme 10



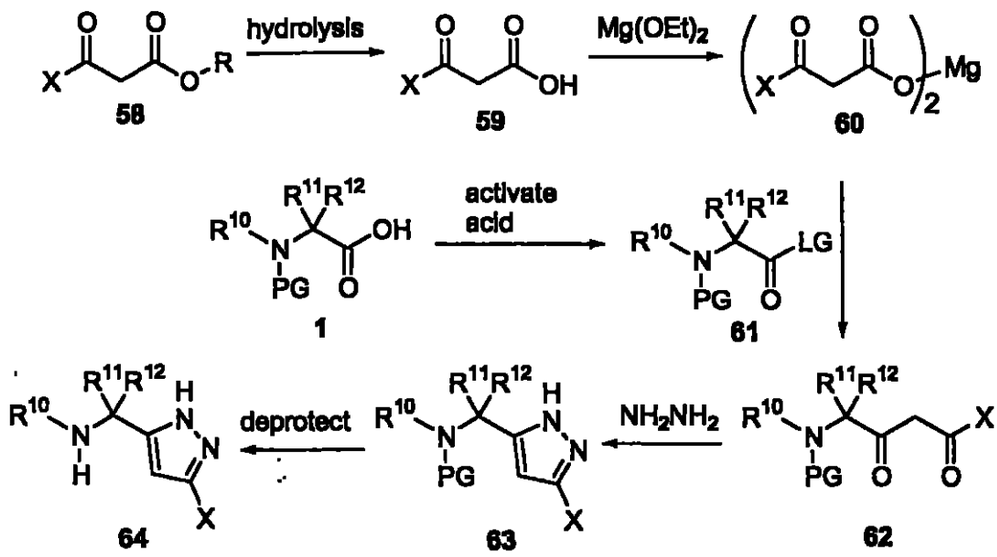
[00509] A general procedure for the synthesis of oxazoles having substituents in the 2- and 4-positions useful for the synthesis of compounds of this invention is shown in Scheme 6. A suitably protected amino acid 1 and beta-keto amine 50 (X = aryl or heteroaryl) are dissolved in a suitable solvent, for example pyridine, and treated with amide coupling reagent, for example BOP reagent, at room temperature. The keto amide 51 thus formed is dehydrated by dissolving in a suitable solvent such as DMF and treating the solution with phosphorous oxychloride at elevated temperature (Sow et al. *J. Org. Chem.* 1990, *55*, 386). The oxazole 52 is deprotected in preparation for acylation of the amine 53, which is outlined in Scheme 17.

Scheme 12



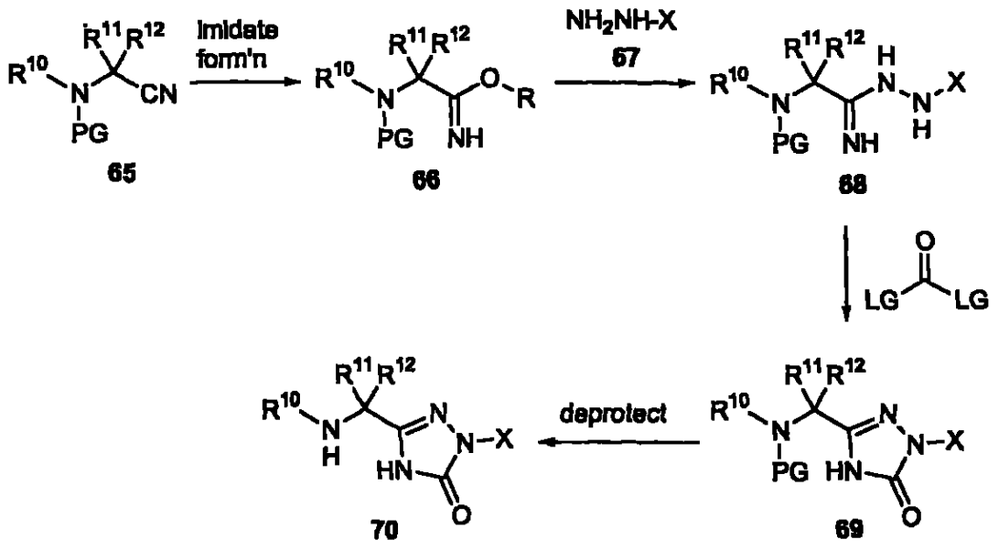
[00511] Suitably substituted pyrazoles useful for the synthesis of compounds of this invention may be synthesized using the procedures shown in Scheme 13 (Shunsaku Ohta et al. *Chem. Pharm. Bull.* **1981**, *29 (10)*, 2762). A suitably substituted β-keto ester **58** (X = aryl or heteroaryl) is dissolved in a suitable solvent and the ester hydrolyzed with, for example, sodium hydroxide. The magnesium salt (**60**) of the beta keto acid **59** is formed by dissolving the acid in a suitable solvent such as methanol and THF followed by addition of magnesium ethoxide. In a separate reaction sequence, the carboxylic acid of a suitably protected amino acid **1** (Y = $R^{10}N(PG)$-) is activated with, for example, carbonyl diimidazole to give the activated amino acid **61** (LG = imidazol-1-yl in this illustration). Compound **60** and **61** are combined in a suitable solvent, for example DMF, to give the beta diketone **62**. Treatment of **62** with hydrazine at elevated temperatures affords the pyrazole **63**. When the amino group of **64** is protected with a CBz moiety, the protecting group may be removed by catalytic hydrogenation using, for example, palladium on carbon and elemental hydrogen to give amine **64**.

Scheme 13



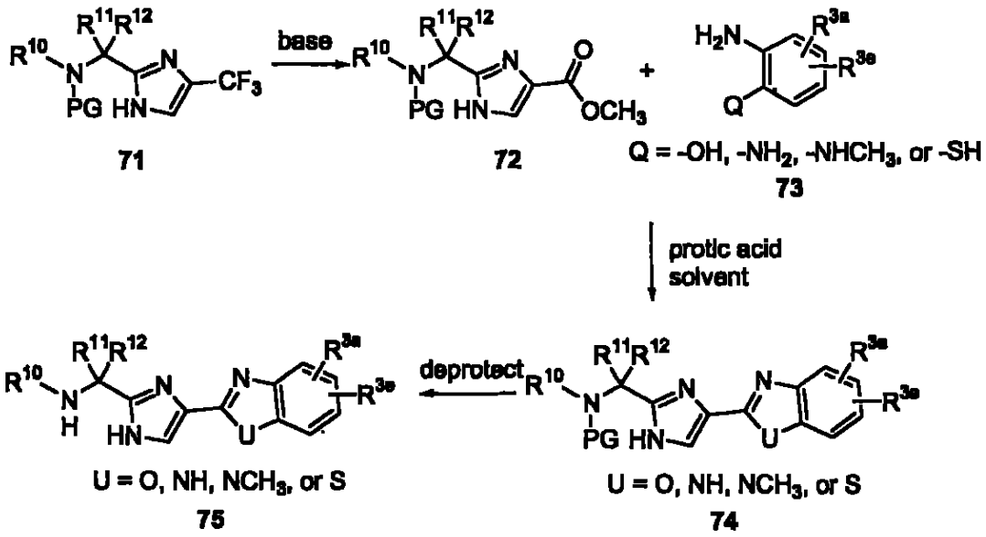
[00512] A general procedure for the formation of substituted triazolones useful for the synthesis of compounds of this invention is shown in Scheme 14. A suitably substituted protected beta-amino nitrile 65 is treated with the sodium salt of an alcohol, for example sodium methoxide, to form the imidate 66. The imidate 66 is reacted with a suitably substituted hydrazine 67 (X = aryl or heteroaryl) to form the amino amidine 68 (Yanagisawa et al. *J. Med. Chem.* 1984, *27(7)*, 849). Treatment of 68 with a bis-activated carbonyl such as carbonyl diimidazole (LG = imidazol-1-yl) provides the triazolone 69. Deprotection of the amino group of 69 is carried out in preparation for acylation of the nitrogen, which is outlined in Scheme 17. For example, when the amine is protected with a CBz moiety, the protecting group may be removed using catalytic hydrogenation using, for example, palladium on carbon and hydrogen or, alternatively, by treatment with HBr in HOAC or neat TFA to give amine 70.

Scheme 14



[00513] The synthesis of imidazoles substituted with fused ring heterocycles in the 4-position is shown in Scheme 15. A suitably protected and functionalized 4-trifluoromethyl imidazole 71 is available according to the chemistry outlined in Scheme 3. The imidazole 71 is dissolved in a suitable solvent such as methanol and heated in the presence of a base such as sodium methoxide. The methyl ester 72 thus formed is dissolved in a suitable solvent, for example, tetrahydrofuran, and combined with an aniline 47 substituted in the ortho position with either hydroxy, amino, mono alkyl amino or thiol. The aniline employed may have additional substituents, R^{3a} and R^{3c}, known to those skilled in the art to be compatible with the reaction conditions. The two reactants are treated with a protic acid, for example, *para*-toluene sulfonic acid, to effect addition of the aniline and subsequent cyclization and dehydration to form the fused heterocycle 74. The amine protecting group is removed in preparation for acylation of the amine, which is outlined in Scheme 17. When the protecting group is a BOC moiety, the amine is de-protected with strong acid such as trifluoroacetic acid or HCl in suitable solvent such as dichloromethane or dioxane to give amine 75 as the bis-TFA salt.

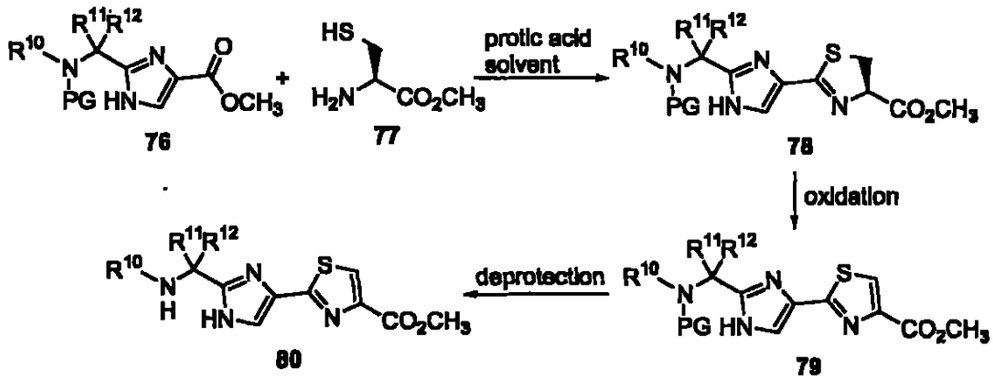
Scheme 15



71 72 73 75 74

[00514] Thiazol-2-yl imidazole derivatives useful for the synthesis of compounds of this invention can be prepared as shown in Scheme 16. A suitably substituted ester 76 and a beta amino thiol such as cysteine methyl ester 77 are combined in a suitable solvent such as tetrahydrofuran and treated with a protic acid such as camphor sulfonic acid. Other beta amino thiols having functional groups compatible with these conditions may be employed in this reaction. The resulting thiazolidine 78 is oxidized to the thiazole 79 using, for example, manganese dioxide. Other suitable oxidants may be employed in this step such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The amino group of 79 is deprotected in preparation for acylation. For example, when the protecting group is a BOC moiety, the amine is deprotected with strong acid such as trifluoroacetic acid in suitable solvent such as dichloromethane to give amine 80 as the bis-TFA salt.

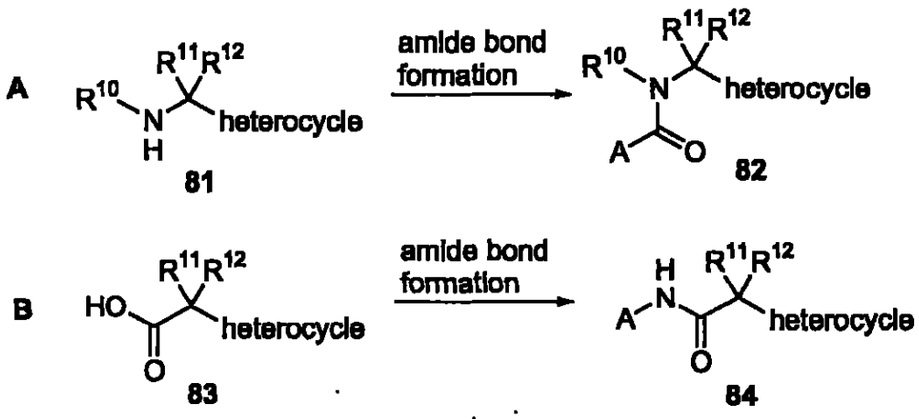
Scheme 16



[00515] Each of the aforementioned reaction Schemes 1-3 and 9-16 produce a heterocycle containing an aminoalkyl side chain suitable for reacting with suitably substituted carboxylic acids, for example, N-Boc tranexamic acid or 4-cyanobenzoic acid, under standard amide bond coupling conditions (Scheme 17A). Reagent combinations commonly employed for this transformation may be used and include, but are not limited to: BOP-reagent and pyridine; EDCI, HOAt, N-methyl morpholine; or EDCI, HOBt, N-methyl morpholine. Solvents suitable for this transformation include, but are not limited to, pyridine, THF and dimethylformamide. Solvent combinations may also be used such as dichloromethane and DMF in ratios suitable to achieve solubility of the reagents employed. Alternately, the amines from Schemes 1-3 and 9-16 can be reacted with suitable substituted alkylating agents or sulfonyl halides, using methods known to one skilled in the art. It should be recognized that additional deprotection steps and further functional group manipulations of compounds obtained via Scheme 17 using methods known in the art will then provide additional compounds of this invention.

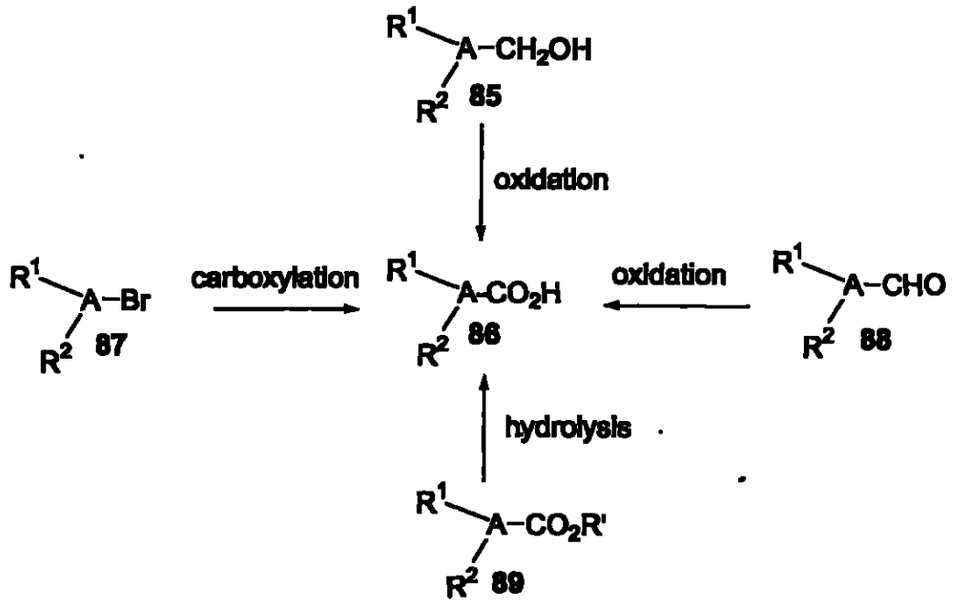
[00516] Alternatively, when the heterocycle contains a aliphatic carboxylic acid containing side chain, amide bond formation may be effected by reaction with a suitably substituted amine or aniline with the reagent combinations described herein (Scheme 17B).

Schemes 17A and 17B



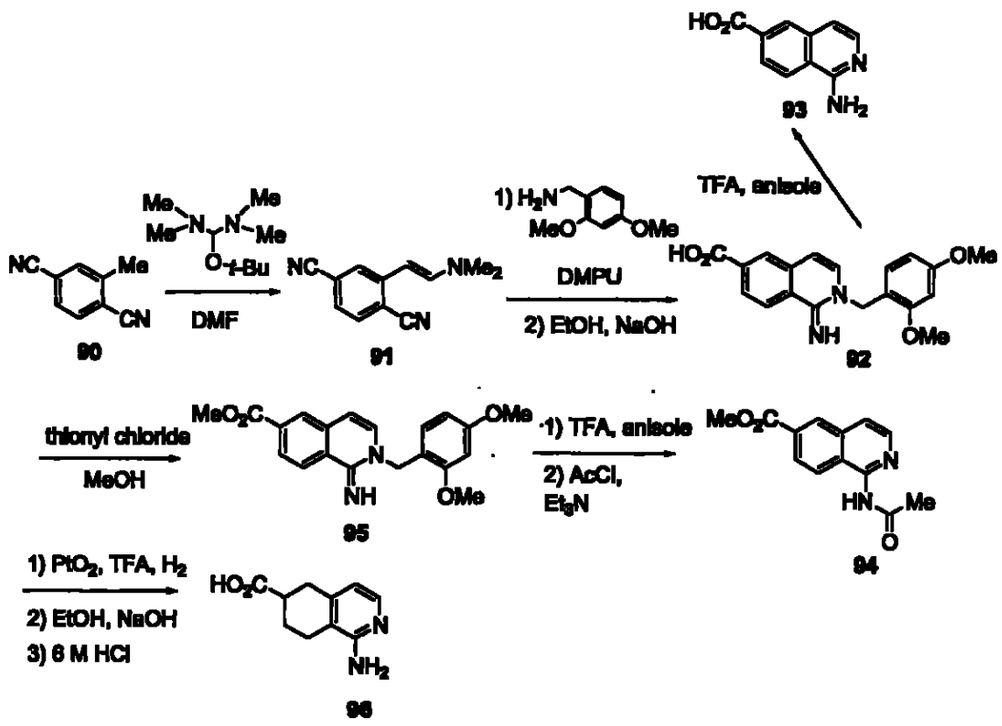
[00517] A suitably substituted carboxylic acid (A-CO_2H) is used in the amide coupling shown in Scheme 17A. Many of these carboxylic acids are commercially available. In case where the carboxylic acids are not commercially available, they can be prepared from the corresponding bromide **87**, alcohol **85**, aldehyde **88**, or ester **89** as shown in Scheme 18 using methods known in the art. The R^1 and R^2 groups can be further manipulated using methods known in the art to provide additional compounds of this invention. For example, the cyano group can be used as R^1, which can be reduced to give CH_2NH_2 with a suitable reducing agent or converted to the amidine by reaction with hydroxylamine, and followed by palladium catalyzed hydrogenation using methods described previously.

Scheme 18



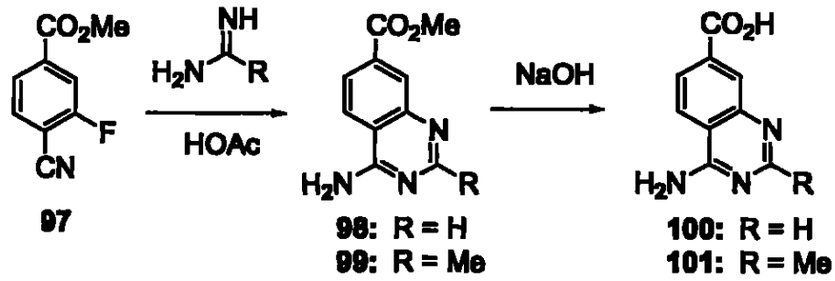
[00518] When A is an isoquinoline moiety a modified procedure from US2004/0077865 is followed. Heating the 2-methyl benzonitrile derivative **90** with 1-(*t*-butoxy)-N,N,N',N'-tetramethylmethanediamine in a suitable solvent such as DMF gives the enamine **91**. Condensation of enamine **91** and 2,4-dimethoxybenzylamine in DMPU at elevated temperatures gives the 1-imino-1,2-dihydroisoquinoline skeleton and subsequent hydrolysis provides **92**. Debenzylation of **92** with anisole in TFA at elevated temperatures provides 1-amino-isoquinoline **93**. When A is a 5,6,7,8-tetrahydroisoquinoline moiety a modified procedure of McEachern *et al.* is followed (*J. Org. Chem.* **2002**, *67*, 7890). Acid **92** is converted to the ester **94**. Debenzylation of **94** with anisole in TFA at elevated temperatures and acetylation with acetyl chloride and triethylamine yields **95**. Hydrogenation over platinum oxide in the presence of TFA provides the 1-amino-5,6,7,8-tetrahydroisoquinoline. Saponification of the ester with NaOH and hydrolysis of the amide under acidic conditions gives **96**.

Scheme 19



[00519] When A is a 4-aminoquinazoline moiety, heating an appropriately substituted ortho-fluoro benzonitrile **97** with formamidine acetate or acetamidine acetate in DMA, according to a modified procedure of Lam (Lam, P.Y. S. *et al. J. Med. Chem.* **2003**, *46*, 4405.), gives 4-aminoquinazoline **98** and **99**. Saponification of the ester under basic conditions provides **100** and **101**.

Scheme 20



[00520] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[00521] Solution ratio expresses a volume relationship, unless stated otherwise. NMR chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel according to Still's method (Still, W. C. *et al. J. Org. Chem.* 1978, *43*, 2923).

[00522] As used throughout the specification, the following abbreviations for chemical reagents apply:

HOAc or AcOH = acetic acid

Bn = benzyl

Bu = butyl

t-Bu = tertiary butyl

Boc = *tert*-butyl oxycarbonyl

BOP reagent = benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate

Brine = saturated aqueous sodium chloride

CSA = camphor sulfonic acid

DMF = dimethylformamide

DMSO = dimethyl sulfoxide

EDCI = 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride

Et = ethyl

EtOH = ethanol

EtOAc = ethyl acetate

Me = methyl

MeOH = methanol

NaOAc = sodium actetate

OAc = acetate

Ph = phenyl

Pr = propyl

i-Pr = isopropyl

i-PrOH = isopropanol

TFA = trifluoroacetic acid

THF = tetrahydrofuran

°C = degrees Celsius

atm = atmosphere

conc. = concentrated

eq = equivalent(s)

h or hr = hour(s)

g = gram(s)

mg = milligram(s)

L = liter(s)

mL = milliliter(s)

µL = microliter(s)

mmol = millimolar

M = molar

meq = milliequivalent(s)

Min = minute(s)

MW = molecular weight

mp = melting point

rt or RT = room temperature

sat or sat'd = saturated

ESI = electrospray ionization mass spectroscopy

HPLC = high performance liquid chromatography

MS = mass spectrometry

LC/MS = liquid chromatography mass spectrometry

HRMS = high resolution mass spectrometry

NMR = nuclear magnetic resonance spectroscopy

TLC = thin layer chromatography

[00523] "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art. One stereoisomer of a compound of Formula I may display superior activity compared with the others. Thus, each stereoisomer of a compound of Formula I is considered to be a part of the present invention. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as described in Wilen, S. H.

Tables of Resolving Agents and Optical Resolutions 1972, 308 or using enantiomerically pure acids and bases. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, *e.g.*, Jacobsen, E. *Acc. Chem. Res.* 2000, *33*, 421-431 or using other enantio- and diastereo-selective reactions and reagents known to one skilled in the art of asymmetric synthesis.

[00524] The following Examples have been prepared, isolated and characterized using the methods disclosed herein. The following Examples demonstrate a partial scope of the invention and are not meant to be limiting of the scope of the invention.

Example 1

(*S*)-4-carbamimidoyl-N-(2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)benzamide, bistrifluoroacetic acid salt

[00525] *Part A: (S)-tert-butyl 2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethylcarbamate*: To a solution of L-N-(Boc)-phenylalanine (750 mg, 3.77 mmol) in EtOH/H_2O (1:1; 7.4 mL) was added with Cs_2CO_3 (650 mg, 1.89 mmol). The reaction was stirred at rt for 1 h. The solvent was removed under vacuum and the resulting salt suspended in DMF (4.7 mL). 2-Bromoacetophenone (1.0 g, 3.77 mmol) was added in a single portion and the reaction stirred at rt for 1.5 h. The reaction was filtered to remove CsBr. The solids were washed with DMF. The combined washings and filtrate were concentrated in *vacuo* to yield a yellow solid (650 mg). The crude intermediate was placed in a flask fitted with a Dean-Stark trap and dissolved in xylenes (10 mL). NH_4OAc (2.64 g, 30 mmol) was added to the flask and the reaction was heated to reflux for 3 h. The reaction was cooled to rt and the solvent removed *in vacuo*. The residue was redissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness to yield 780 mg of the desired product (57% yield). MS 364.2 $(M+H)^+$.

[00526] Alternatively, the keto ester intermedite and 10 equivalents of NH_4OAc were dissolved in ethanol and heated to 160 °C in a sealed tube for 30 min using microwave irradiation. The reaction was cooled to rt, the ethanol was evaporated in *vacuo* and the residue was redissolved in EtOAc. The organic layer

was washed with ½ saturated brine (2 times), dried over $MgSO_4$ and evaporated to dryness. The crude product thus formed was sufficiently pure to carry on to the next step.

[00527] *Part B: (S)-2-Phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine bis-trifluoroacetic acid salt*: The product from Example 1 Part A (100 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (2.8 mL) and treated with neat TFA (0.2 mL, 10% v/v). The reaction was stirred at rt for 16 h. The solvent and TFA were removed in *vacuo*. The residue was redissolved in methanol. The solvent was removed *in vacuo*, the residue was re-dissolved in MeOH and the solvent wad evaporated *in vacuo* to yield 124 mg (92% yield) of crude amine as the bis-TFA salt. MS 262.2 $(M-H)^-$.

[00528] *Part C: (S)-4-carbamimidoyl-N-(2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)benzamide, bistrifluoroacetic acid salt*: The product from Example 1 Part B (124 mg, 0.25 mmol) and 4-amidinobenzoic acid hydrochloride (94 mg, 0.47 mmol) were dissolved in anhydrous pyridine (2 mL). BOP reagent (249 mg, 0.56 mmol) was added and the reaction was stirred at rt for 16 h. The solvent was removed in *vacuo* and the residue redissolved in MeOH/H_2O (9:1) containing 0.1% TFA. The solution was filtered and the title compound was isolated by prep HPLC to yield 9.2 mg of the desired product (3% yield). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 3.37 (dd, J = 8.5 and 13 Hz, 1H), 3.46 (dd, J = 8.5 and 13 Hz, 1H), 5,48 (app t, J = 8.2 Hz, 1H), 7.14-7.21 (m, 5H), 7.34-7.41 (m, 3H), 7.56 (m, 2H), 7.68 (s, 1H), 7.80 (d, J = 8.2 Hz), 7.96 (d, J = 8.2 Hz, 2H): HRMS $(M + H)^+$ for $C_{25}H_{23}N_5O$, calcd m/z: 410.1981, obs: 410.1974.

Example 2

(*S*)-4-(aminomethyl)-N-(2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt

[00529] *Part A: (S)-tert-Butyl (4-((2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)carbamoyl)cyclohexyl)methylcarbamate*: The product from Example 1 Part B (75 mg, 0.15 mmol) and N-(Boc)-tranexamic acid (75 mg, 0.29 mmol) were dissolved in pyridine (1.7 mL). BOP reagent (152 mg, 0.344 mmol) was added and the reaction was stirred at rt for 12 h. The reaction was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4,

filtered and evaporated in *vacuo*. The crude product was carried on to the next step without further purification. MS 503.2 $(M+H)^+$.

[00530] Alternately, the product from Example 1 Part B was coupled with 1.0 equivalents of N-Boc-tranexamic acid, 1.2 equivalents HOAt, 5.0 equivalents of N-methylmorpholine, and 1.2 equivalents of EDCI. The amine, N-Boc-tranexamic acid and HOAt are dissolved in DMF. N-Methylmorpholine is added followed by EDCI. The reaction is stirred at rt for 2 and 16 h. The reaction is diluted with EtOAc, washed with ½ saturated brine (4-6 times), dried over $MgSO_4$, filtered and evaporated to dryness to give the crude product.

[00531] *Part B: (S)-4-(aminomethyl)-N-(2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt*: The product from Example 2 Part A (100 mg) was dissolved in 30% TFA in CH_2Cl_2 (2.0 mL). The reaction was stirred at rt for 3 h. The reaction was diluted with toluene and dried in *vacuo*. The residue was re-dissolved in toluene and solution evaporated to dryness. The crude product was re-dissolved in MeOH/H_2O (9:1) containing 0.1% TFA and the title compound was isolated by prep HPLC (46 mg as the bis-TFa salt,49% yield). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.02-1.11 (m, 2H), 1.32-1.45 (m, 2H), 1.54-1.61 (m, 1H), 1.80 (br d, J = 12.1 Hz, 1H), 1.86 (br d, J = 11.5 Hz, 3H), 2.28 (dt, J = 12.1, 3.30 Hz, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.28-3.33 (dd, 1H, obscured by CH_3OH peak), 3.38 (dd, J = 13.5, 8.0 Hz), 5.31 (t, J = 8.25 Hz, 1H), 7.18 (d, J = 7.15 Hz, 2 H), 7.22-7.30 (m, 3H), 7.43-7.50 (m, 3H), 7.62 (app d, J = 6.6 Hz, 2H), 7.75 (s, 1H): MS 403.2 $(M + H)^+$.

Example 25

(S)-Ethyl 2-(4-(2-(1-(4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetate, bistrifluoroacetic acid salt

[00532] *Part A: Ethyl 4-acetyl-phenylacetate*: Ethyl bromoacetate (1.70 g, 10.2 mmol), tris-(1-naphthylene)phosphine (379 mg, 0.93 mmol) and tribasic potassium phosphate (10.8 g, 51 mmol) were placed in a flask. The flask was evacuated and back-filled with argon. A solution of 4-acetylphenylboronic acid (2.0 g, 12.2 mmol) in anhyd THF (40 mL) was added to the flask. The reaction was stirred at rt for 16 h.

The reaction was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was pre-adsorbed on to SiO_2 and the product isolated via SiO_2 chromatography to yield 616 mg (29%) of ethyl 4-acetyl-phenylacetate. MS 207.1 $(M+H)^+$.

[00533] *Part B*: *Ethyl 2-(4-(2-bromoacetyl)phenyl)acetate*: Ethyl 4-acetyl-phenylacetate from **Example 25** Part A (489 mg, 2.4 mmol) was dissolved in CH_2Cl_2. Bromine (379 mg, 2.4 mmol) was added dropwise. The reaction was stirred at rt for 16 h. The reaction had decolorized from rust red to light yellow. The solvent was evaporated in *vacuo* to yield 680 mg (99%) of ethyl 2-(4-(2-bromoacetyl)phenyl)acetate as a light yellow oil. The product was used in the next step without further purification. MS 287.0 and 289.0 of equal intensities $(M+H)^+$.

[00534] *Part C: (S)-Ethyl 2-(4-(2-(1-(tert-butoxycarbonyl)-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetate*: N-(Boc)-phenylalanine (633 mg, 2.38 mmol) was dissolved in DMF (2.0 mL). Cs_2CO_3 (775 mg, 1.19 mmol) was added to the flask in a single portion, and the reaction was stirred for 1 h. A solution of ethyl 2-(4-(2-bromoacetyl)phenyl)acetate from **Example 25** Part B (680 mg, 2.38 mmol) in DMF (2.0 mL) was added to the reaction vessel, and the reaction was stirred at rt for 16 h. The solids were filtered off and rinsed with DMF. The organic layers were combined and evaporated to dryness. The residue was re-dissolved in EtOAc and washed with a solution of 1:1 water and brine, dried over $MgSO_4$, filtered and evaporated to yield 1.03 g of a light tan solid. The solid was re-dissolved in xylenes (14 mL). NH_4OAc (3.42 g, 44 mmol) was added, and the flask fitted with a Dean-Stark trap. The reaction was heated to reflux for 5 h with removal of water. The reaction was cooled to rt, and the solvent removed in *vacuo*. The residue was re-dissolved in EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and evaporated to yield 951 mg (96%) of a light tan solid. MS 450.1 $(M+H)^+$.

[00535] *Part D: (S)-Ethyl 2-(4-(2-(1-amino-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetate*: The product from **Example 25** Part C (951 mg, 2.12 mmol) was treated according to the procedure described for **Example 1** Part B to yield 1.14 g (100%) of a dark brown glass, which was used without further purification in the next step. MS 333.1 $(M-NH_2)^+$.

[00536] *Part E: (S)-Ethyl 2-(4-(2-(1-(4-((tert-butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetate*: The product from Example 25 Part D (729 mg, 1.26 mmol), N-(Boc)-tranexamic acid (325 mg, 1.26 mmol) and HOAt (206 mg, 1.51 mmol) were dissolved in DMF (6.3 mL). N-methylmorpholine (637 mg, 6.3 mmol) was added followed by EDCI (289 mmol, 1.51 mmol). The reaction was stirred at rt for 16 h, diluted with EtOAc, washed with a 1:1 mixture of water and brine, dried over $MgSO_4$, filtered and evaporated to yield 732 mg (99%) of product, which was used in the next step without further purification. MS 589.1 $(M+H)^+$.

[00537] *Part F: (S)-Ethyl 2-(4-(2-(1-(4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetate, bistrifluoroacetic acid salt*: The product from Example 25 Part E (99 mg, 0.17 mmol) was treated with TFA according to the procedure described for Example 1 Part B. The product was isolated by prep HLPC to yield 61 mg (50%) of the title compound as the bis-TFA salt. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.02-1.11 (m, 2H), 1.24 (t, J = 7.15 Hz, 3H), 1.32-1.45 (m, 2H), 1.53-1.61 (m, 1H), 1.80 (br d, J = 12.6 Hz, 1H), 1.86 (br d, J = 11.0 Hz, 3H), 2.28 (tt, J = 12.4, 3.0 Hz, 1H), 2.775 (d, J = 7.15 Hz, 2H), 3.28-3.32 (dd, obscured by MeOH peak), 3.38 (dd, J = 13.5, 8.0 Hz, 1 H), 3.70 (s, 2H), 4.145 (q, J = 7.15 Hz, 2H), 5.31 (t, J = 8.5 Hz, 1H), 7.175 (d, J = 7.15 Hz, 2H), 7.22-7.30 (m, 3H), 7.41 (d, J = 8.25, 2H), 7.59 (d, J = 8.25 Hz; 2H), 7.74 (s, 1H). HRMS $(M + H)^+$ for $C_{29}H_{36}N_4O_3$, calcd m/z: 489.2866, obs: 489.2861.

Example 26

(S)-2-(4-(2-(1-(4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetic acid, bistrifluoroacetic acid salt

[00538] (S)-Ethyl 2-(4-(2-(1-(4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetate bis trifluoroacetic acid salt from Example 25 (30 mg, 0.042 mmol) was dissolved in MeOH (2 mL) and treated with 1 N NaOH (0.2 mL). The reaction was stirred at rt for 16 h. The solvent was removed in *vacuo* and the residue re-dissolved in MeOH/H_2O (9:1) containing 0.1% TFA and then purified by prep HPLC to yield 22 mg of the title compound as its bis –TFA salt (76% yield). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.02-1.11 (m, 1H), 1.31-1.45 (m, 2H),

1.53-1.61 (m, 1H), 1.79 (br d, J = 12.1 Hz, 1H), 1.865 (br d, J = 12.1 Hz, 3H), 2.28 (tt, J = 3.2 and 12.1 Hz, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.28-3.32 (dd, obscured by MeOH peak), 3.375 (dd, J = 8.0 and 13.4 Hz, 1 H), 3.67 (s, 2H), 5.31 (t, J = 8.25 Hz, 1H), 7.175 (d, J = 6.6 Hz, 2H), 7.22-7.30 (m, 3H), 7.42 (d, J = 8.25 Hz, 2H), 7.59 (d, J = 8.25 Hz, 2H), 7.74 (s, 1H). HRMS $(M + H)^+$ for $C_{27}H_{32}N_4O_3$, calcd m/z: 461.2553, obs: 461.2572.

Example 27

(*S*)-4-(aminomethyl)-N-{1-[(4-carbamoylmethyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-cyclohexanecarboxamide, bistrifluoroacetic acid salt

[00539] *Part A: (S)-2-(4-(2-(1-(4-((tert-Butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)phenyl)acetic acid*: The product from **Example 25** Part E (200 mg, 0.34 mmol) was dissolved in MeOH (3 mL) and treated with 1 N NaOH (0.34 mL). The reaction was stirred at rt for 16 h. The solvent was removed in *vacuo*. The residue was re-dissolved in MeOH/H_2O (9:1) containing 0.1% TFA. The product was isolated by prep HPLC (90 mg, 47%). MS 561.1 $(M+H)^+$.

[00540] *Part B: (S)-tert-Butyl (4-((1-(4-(4-(2-amino-2-oxoethyl)phenyl)-1H-imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate*: The product from **Example 27** Part A (33 mg, 0.060 mmol) and HOAt (9.7 mg, 0.071 mmol) were dissolved in DMF (1 mL). N-Methylmorpholine (18.2 mg, 0.18 mmol) and EDCI (13.6 mg, 0.071 mmol) were added sequentially. The reaction as stirred for 30 min at rt. Conc. aqueous ammonia (5 drops from a Pasteur pipet) was added and the reaction stirred at rt for 16 h. The reaction was diluted with EtOAc and washed with a 1:1 mixture of water and brine (5x), 1 N aqueous HCl and brine, dried over $MgSO_4$, filtered and dried in *vacuo*. The residue was re-dissolved in MeOH/H_2O (9:1) containing 0.1% TFA, and the product isolated by prep HPLC to yield 9 mg (22%). MS 560.1 $(M+H)^+$.

[00541] *Part C: (S)-N-(1-(4-(4-(2-amino-2-oxoethyl)phenyl)-1H-imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)-cyclohexanecarboxamide, bistrifluoroacetic acid salt*: The product from **Example 27** Part B (9 mg, 0.016 mmol) was treated with TFA

according to the procedure described for Example 1 Part B to provide the title compound (11 mg, 99%). ^{1}H-NMR (500 MHz, d$_4$-MeOH) δ 1.02-1.11 (m, 2H), 1.28-1.44 (m, 2H), 1.57 (m, 1H), 1.79 (br d, J = 12.6 Hz, 1H), 1.85 (br d, J = 11 Hz, 3H), 2.28 (tt, J = 3.0, 12.1 Hz, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.28-3.32 (dd, obscured by MeOH), 3.375 (dd, J = 8.0, 13.0 Hz, 1H), 3.57 (s, 2H), 5.31 (t, J = 8.2 Hz, 1H), 7.175 (d, J = 7.2 Hz, 2H), 7.22-7.30 (m, 3H), 7.43 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.74 (s, 1H); HRMS (M + H)$^+$ for $C_{27}H_{33}N_5O_2$, calcd m/z: 460.2713, obs: 460.2714.

Example 28

4-(2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzamide, bistrifluoroacetic acid salt

[00542] *Part A: tert-Butyl)trans-4-(((S)-1-(4-(4-carbamoylphenyl)-1H-imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate*: tert-Butyl (*trans*-4-(((S)-1-(4-(4-cyanophenyl)-1H-imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate formed from 2-bromo-4'-cyanoacetophenone using the procedures from **Example 1** Part A-B and **Example 2** Part A (117 mg ,0. 22 mmol) was dissolved in DMSO (2 mL) and treated with K_2CO_3 (90.0 mg, 0.65 mmol) under argon. 30% H_2O_2 in water (0.8 mL, 2.4 mmol) and magnesium oxide (44 mg, 1.11 mmol) were added sequentially to the reaction. The reaction was stirred at rt for 4 h. The reaction was diluted with EtOAc, washed with 1 N HCl and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The product (109 mg, 90% yield) was isolated as a yellow solid. MS 546.3 (M+H)$^+$.

[00543] *Part B: 4-(2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzamide, bistrifluoroacetic acid salt*: The product from **Example 28** Part A (109 mg, 0.20 mmol) was treated with TFA according to the procedure described for **Example 2** Part B. The product was isolated by prep HLPC to yield 17.3 mg of the title compound (20 %).. ^{1}H NMR (500 MHz, d$_4$-MeOH) δ 0.36 (m, 2 H), 0.68 (m, 2 H), 0.87 (m, 1 H), 1.14 (m, 3 H), 2.07 (d, J = 7.15 Hz, 2 H), 2.63 (m, 2H), 4.61 (t, J = 8.25 Hz, 1 H), 6.47 (d, J = 7.15 Hz, 2 H) ,6.53 (t, J = 7.42 Hz, 1 H) ,6.58 (t, J = 7.15 Hz, 2 H), 7.04 (d, J = 8.25 Hz, 2 H), 7.14 (s, 1 H), 7.28 (d, J

= 8.25 Hz, 2 H); HRMS $(M + H)^+$ for $C_{26}H_{31}N_5O_2$, calcd m/z: 446.2556, obs: 446.2570.

Example 29

3-(2-((S)-1-(4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzamide, bistrifluoroacetic acid salt

[00544] The title compound was synthesized by appropriate application of the procedures described for **Example 28**. ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.06 (m, 2 H), 1.39 (m, 2 H), 1.57 (m, 1 H), 1.80 (d, J = 12.10 Hz, 1 H), 1.86 (d, J = 11.55 Hz, 3 H), 2.28 (tt, J= 12.10, 3.30 Hz, 2 H), 2.77 (d, J = 7.15 Hz, 2 H), 3.34 (d, J = 8.25 Hz, 1 H), 3.39 (dd, J = 13.40, 8.25 Hz, 1 H), 3.98 (s, 1 H), 5.34 (t, J = 8.25 Hz, 1 H), 7.19 (d, J = 6.60 Hz, 2 H), 7.24 (t, J = 7.15 Hz, 1 H), 7.29 (t, J = 7.15 Hz, 2 H), 7.60 (t, J = 7.70 Hz, 1 H), 7.82 (m, J = 5.50 Hz, 2 H), 7.93 (d, J = 8.25 Hz, 1 H) 8.18 (s, 1 H); MS 446.2 $(M+H)^+$.

Example 30

4-(2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)-N-methylbenzamide, bistrifluoroacetic acid salt

[00545] ***Part A: 4-(2-((S)-1-(trans)-4-((tert-Butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzoic acid***: Methyl 4-(2-((S)-1-(*trans*-4-((tert-butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzoate formed from 2-bromo-4'-carboxymethylacetophenone using the procedures from **Example 1** Part A-B and **Example 2** Part A (162 mg, 0. 28 mmol) was dissolved in MeOH (5 ml) and EtOAc (1 mL). 1 N NaOH (2 mL) and magnesium oxide (112 mg, 2.8 mmol) were added sequentially and the mixture was stirred for 5 hrs at rt. The solvent was evaporated to dryness in *vacuo*. The residue was diluted with water and treated with 1 N HCl. The resulting solution was diluted with EtOAc, washed with brine and dried over $MgSO_4$, filtered and evaporated to yield 75 mg (60 % yield) of a clear glass. MS 548.0 $(M+H)^+$.

[00546] *Part B: tert-Butyl (trans)-4-(((S)-1-(4-(4-(methylcarbamoyl)phenyl)-1H-imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate*: The product from **Example 30** Part A (45 mg, 0.08 mmol) and methylamine (0.2 mL, 0.09 mmol) were treated under the conditions described in **Example 2** Part B with the substitution of HOBt for HOAt. The resulting yellow oil (44.0. mg, 93% yield) was carried to the next step without further purification. MS 560.1 $(M+H)^+$

[00547] *Part C: 4-(2-((S)-1-(trans)-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)-N-methylbenzamide, bistrifluoroacetic acid salt*: The product from **Example 30** Part B (44.0 mg, 0.079 mmol) was treated with TFA according the procedure described for **Example 2** Part B. The resulting residue was re-dissolved in MeOH/ H_2O (9:1) containing 0.1% TFA and isolated by prep HPLC to yield 1.0 mg of the title compound (3%). ^1H NMR (500 MHz, d_4-MeOH) δ 1.05 (m, 1 H), 1.39 (ddd, J = 30.24, 12.92, 3.02 Hz, 1 H), 1.55 (m, J = 12.10 Hz, 1 H), 1.79 (m, 1 H), 1.86 (d, J = 11.00 Hz, 1 H), 2.26 (m, 1 H), 2.77 (d, J = 7.15 Hz, 1 H), 2.92 (s, 1 H), 3.15 (m, 1 H), 3.3 (m, 2H), 5.29 (t, J = 8.25 Hz, 1 H), 7.16 (d, J = 7.15 Hz, 1 H), 7.23 (t, J = 7.15 Hz, 1 H), 7.28 (t, J = 7.15 Hz, 1 H), 7.72 (d, J = 8.25 Hz, 1 H), 7.86 (s, 1 H), 7.92 (d, J = 8.80 Hz, 1 H); HRMS $(M + H)^+$ for $C_{27}H_{33}N_5O_2$, calcd m/z: 460.2713, obs: 460.2735.

Example 31 (S)-4-(2-(1-*trans*-(4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)-N,N-dimethylbenzamide, bistrifluoroacetic acid salt

[00548] The title compound was synthesized by appropriate application of the procedures described for the synthesis of **Example 30**. ^1H NMR (500 MHz, d_4-MeOH) δ 1.06 (m, 2 H), 1.39 (m, 2 H), 1.57 (m, 1 H), 1.81 (d, J = 14.85 Hz, 1 H), 1.86 (d, J = 10.45 Hz, 3 H), 2.28 (tt, J = 12.30, 3.30 Hz, 1 H), 2.77 (d, J = 7.15 Hz, 2 H), 3.01 (s, 3 H), 3.12 (s, 3 H), 3.39 (dd, J = 13.30, 8.24 Hz, 1 H), 5.31 (t, J = 8.25 Hz, 1 H), 7.18 (d, J = 7.15 Hz, 2 H), 7.24 (t, J = 7.15 Hz, 1 H), 7.29 (t, J = 7.42 Hz, 2 H), 7.55 (d, J = 8.25 Hz, 2 H), 7.72 (d, J = 8.25 Hz, 2 H), 7.85 (s, 1 H); HRMS $(M + H)^+$ for $C_{28}H_{35}N_5O_2$, calcd m/z: 474.2870, obs: 474.2875.

Example 32

***trans*-N-((S)-1-(4-(1H-benzo[d]imidazol-2-yl)-1H-imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)cyclohexanecarboxamide, tristrifluoroacetic acid salt**

[00549] *Part A: (S)-tert-Butyl 2-phenyl-1-(4-(trifluoromethyl)-1H-imidazol-2-yl)ethylcarbamate*: To a solution of sodium acetate (0.88 g, 6.44 mmol) in 3 mL of water was added 1,1-dibromotrifluoroacetone (0.87 g, 3.22 mmol). The mixture was heated at 90 °C under N_2 for 30 min. It was cooled to 0 °C and a solution of (*S*)-(-)-2-(t-butoxycarbonylamino)-3-phenylpropanal (1.73 g, 2.93 mmol) in 15 mL of methanol was added, followed by concentrated ammonium hydroxide (4 mL of concentrated solution). The resulting mixture was stirred at RT under N_2 for 12 h. The solvent was removed and water was added. The precipitate was filtered and then re-dissolved in EtOAc. The EtOAc solution was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give 0.80 g of the desired product as an off-white solid (76.9% yield). MS, 356.30 $(M+H)^+$.

[00550] *Part B: (S)-tert-Butyl 2-phenyl-1-(4-(trimethoxymethyl)-1H-imidazol-2-yl)ethylcarbamate*: The product from Example 32 Part A (0.1 g, 0.4 mmol) was dissolved in MeOH (2 mL) and treated with NaOMe (25% wt in MeOH, 1.7 mL, 7.4 mmol). The reaction mixture was heated using microwave irradiation in a sealed tube for 5 min at 100 °C. Upon cooling to rt, the solvent was removed under vacuum, and the residue dissolved in EtOAc (15 mL). The solution was washed with H_2O, brine, dried over Na_2SO_4, filtered, and evaporated to dryness to yield a brown gum (0.15 g). MS 392.1 $(M+H)^+$.

[00551] *Part C: tert-Butyl (trans-4-(((S)-1-(4-(1H-benzo[d]imidazol-2-yl)-1H-imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate*: The crude intermediate from Example 32 Part B was dissolved in THF (2 mL). 1,2-Phenylenediamine (41 mg, 0.38 mmol) and *p*-toluenesulfonic acid monohydrate (7.3 mg, 0.038 mmol) were added to the reaction. The reaction was stirred at rt for 6 h and the solvent removed in *vacuo*. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography (silica gel, 0-100%

EtOAc in hexane gradient) to yield 59 mg (37%), as a yellow solid. HRMS m/z Calc'd for $C_{23}H_{26}N_5O_2$ $[M+H]^+$: 404.2087. Found 404.2079.

[00552] *Part D: trans-N-((S)-1-(4-(1H-benzo[d]imidazol-2-yl)-1H-imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt*: The product from Example 32 Part C (59 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (0.7 mL) and treated with neat TFA (0.3 mL, 30% v/v). The reaction was stirred at rt for 1 h. The solvent and TFA were removed in *vacuo*. The residue was redissolved in DMF (1 mL). Et_3N (0.073 mL, 0.53 mmol), *N*-Boc-tranexamic acid (42 mg, 0.16 mmol), HOBt (0.03 g, 0.23 mmol), and EDCI (43 mg, 0.23 mmol) were added and the reaction was stirred at rt for 4 h. EtOAc (15 mL) was added, followed by H_2O (10 mL). The separated organic phase was washed with water, brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (0.7 mL) and treated with neat TFA (0.3 mL, 30% v/v). After 40 min. at rt, the reaction was concentrated. Purification by Prep HPLC gave 66 mg (56 %) of the title compound. ^{1}H-NMR (400 MHz, CD_3OD) δ 0.99-1.09 (m, 2 H), 1.27-1.49 (m, 2 H), 1.54-1.60 (m, 1 H), 1.69-1.72 (m, 1 H), 1.82-1.85 (m, 3 H), 2.16-2.23 (m, 1 H), 2.76 (d, J = 7.0 Hz, 2 H), 3.20 (dd, J = 8.8, 13.6 Hz, 1 H), 3.46 (dd, J = 6.6, 13.6 Hz, 1 H), 5.35 (dd, J = 7.0, 8.8 Hz, 1 H), 7.16-7.26 (m, 5 H), 7.54-7.58 (m, 2 H), 7.72-7.76 (m, 2 H), 8.04 (s, 1 H); HRMS m/z Calc'd for $C_{26}H_{31}N_6O$ $[M+H]^+$: 443.2559. Found 443.2545.

[00553] Examples 33-35 listed in Table 2 were similarly synthesized by appropriate application of the procedures described for Example 32.

Example 36

Methyl 2-(2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)thiazole-4-carboxylate, bistrifluoroacetic acid salt

[00554] *Part A: Methyl 2-(2-((S)-1-(tert-butoxycarbonyl)-2-phenylethyl)-1H-imidazol-4-yl)-4,5-dihydrothiazole-4-carboxylate*: (S)-tert-Butyl 2-phenyl-1-(4-(trifluoromethyl)-1H-imidazol-2-yl)ethylcarbamate produced in Example 32 Part A (0.43 g, 1.21 mmol) was dissolved in MeOH (5 mL). NaOMe (25%wt in MeOH, 5.5

mL, 24.2 mmol) was added. The reaction mixture was heated for 42 h at 60 °C, then cooled to rt. The solvent was removed under vacuum, and the residue dissolved in EtOAc (50 mL). The solution was washed with H_2O, brine, dried over Na_2SO_4, filtered and evaporated to dryness to yield a brown gum (0.54 g). A portion of the crude intermediate (0.19 g) was dissolved in THF (5 mL). L-cysteine methyl ester hydrochloride (0.073 g, 0.43 mmol) and CSA (0.01 g, 0.043 mmol) were added to the reaction. The reaction was stirred at rt for 22 h and the solvent was removed *in vacuo*. The residue was purified by flash chromatography to yield 0.022 g of the desired product (12%) as a yellow solid. MS 431.08 $(M + 1)^+$.

[00555] *Part B: Methyl 2-(2-((S)-1-(tert-butoxycarbonyl)-2-phenylethyl)-1H-imidazol-4-yl)thiazole-4-carboxylate*: The product from Example 36 Part A (0.022 g, 0.051 mmol) was dissolved in toluene (1 mL) and treated with MnO_2 (0.067 g, 0.77 mmol). The reaction was stirred at rt for 5 h. The reaction mixture was filtered, and the filter cake washed with EtOAc. The combined filtrates were concentrated to dryness. The residue was purified by flash chromatography to yield 0.017 g of the triazole (78%) as a white solid. HRMS m/z Calc'd for $C_{21}H_{25}N_4O_5S$ $[M + H]^+$: 429.1597. Found 429.1586.

[00556] *Part C: Methyl 2-(2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)thiazole-4-carboxylate, bistrifluoroacetic acid salt*: The product from Example 36 Part B was deprotected with TFA, coupled with N-(Boc)-tranexamic acid, and then deprotected following by the same procedures described in Example 32 Part D to give the title compound, after purification by Prep HPLC (0.014 g, 50 %). ^{1}HNMR (400 MHz, CD_3OD) δ 0.96-1.10 (m, 2 H), 1.27-1.47 (m, 2 H), 1.51-1.61 (m, 1 H), 1.72-1.89 (m, 4 H), 2.18-2.28 (m, 1 H), 2.76 (d, J = 7.0 Hz, 2 H), 3.25-3.35 (m, 2 H), 3.94 (s, 3 H), 5.31 (t, J = 7.9 Hz, 1 H), 7.17-7.28 (m, 5 H), 7.98 (s, 1 H), 8.43 (s, 1 H); HRMS m/z Calc'd for $C_{24}H_{30}Cl_2N_5O_3S$ $(M + H)^+$: 468.2069. Found 468.2063.

Example 37

Methyl 2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxylate, bistrifluoroacetic acid salt

[00557] *Part A: (S)-Methyl 2-(1-amino-2-phenylethyl)-1H-imidazole-4-carboxylate*: The product formed in **Example 32** Part B (492 mg, 1.43 mmol) was treated according to the procedure described for **Example 1** Part B to yield 350 mg of the product (99 %). MS 244.22 $(M-1)^-$.

[00558] *Part B: Methyl 2-((S)-1-trans)-4-((tert-butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxylate*: The product formed in **Example 37** Part A (350 mg, 1.4 mmol) was coupled with N-(Boc)-tranexamic acid according to the procedure described for **Example 2** Part A to yield 290 mg of the product (43 %). MS 485.22 $(M+H)^+$.

[00559] *Part C: Methyl 2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxylate, bistrifluoroacetic acid salt*: The product formed in **Example 37** Part B (290 mg,0.60 mmol) was treated according to the procedure described for **Example 2** Part B to yield the title compound (138 mg, 49 %). ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.05 (ddd, J = 12.51, 8.66, 4.12 Hz, 3 H) 1.36 (ddd, J = 29.14, 12.65, 3.30 Hz, 3 H) 1.56 (dd, J = 7.15, 3.85 Hz, 1 H) 1.75 (d, J = 12.10 Hz, 1 H) 1.84 (dd, J = 10.17, 2.47 Hz, 4 H) 2.21 (m, 1 H) 2.63 (d, J = 9.35 Hz, 1 H) 2.76 (d, J = 7.15 Hz, 3 H) 3.24 (dd, J = 7.97, 2.47 Hz, 3 H) 3.88 (s, 4 H) 5.24 (t, J = 7.97 Hz, 1 H) 7.12 (d, J = 7.15 Hz, 3 H) 7.20 (t, J = 7.15 Hz, 1 H) 7.25 (m, 3 H) 7.86 (s, 1 H) ; MS 385.33 $(M+H)^+$.

Example 38

2-((S)-1-(*trans*-4-(Aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxylic acid, bistrifluoroacetic acid salt

[00560] *Part A: 2-((S)-1-(trans)-4-((tert-Butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxylic acid*: The product from **Example 37** Part B (290 mg, 0.62 mmol) was dissolved in a solution of MeOH (2 mL) and 1 N NaOH (4 mL) and stirred for 72 hrs at rt. The solvent was evaporated to dryness. The residue was diluted with water and treated with 1 N HCl. The resulting solution was diluted with EtOAc , washed with brine, dried over $MgSO_4$, filtered and evaporated to yield 138 mg of the acid (49%). MS 471.05 $(M+1)^+$.

[00561] *Part B: 2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxylic acid, bistrifluoroacetic acid salt*: The product from **Example 38** Part A (50 mg, 0.11 mmol) was treated with the TFA according the procedure described for Example 2 Part B . The resulting residue was re-dissolved in MeOH/ H_2O (9:1) containing 0.1% TFA and isolated by prep HPLC to yield 17.1 mg of the title compound (44%). ^{1}H NMR (500 MHz, d_4-MeOH) δ 0.93 (m, 3 H), 1.24 (m, 3 H), 2.12 (m, 1 H), 2.64 (d, J = 6.87 Hz, 3 H), 2.73 (s, 1 H), 2.86 (s, 1 H), 3.13 (dd, J = 13.75, 8.25 Hz, 1 H), 3.2(m, 2H), 7.01 (d, J = 6.87 Hz, 3 H), 7.11 (d, J = 7.33 Hz, 1 H), 7.15 (t, J = 7.33 Hz, 3 H), 7.81 (s, 1 H); HRMS $(M + H)^+$ for $C_{20}H_{26}N_4O_3$, calcd m/z: 371.2083, obs: 371.2072.

Example 39

Ethyl 2-(2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxamido)acetate, bistrifluoroacetic acid salt

[00562] *Part A: Ethyl 2-(2-((S)-1-(trans-4-((tert-butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxamido)acetate*: The product from **Example 38** Part A (30.0 mg, 0.06 mmol) and ethyl 2-aminoacetate (10 mg, 0.09mmol) were treated under the conditions described in **Example 2** Part A with the substitution of HOBt (10 mg, 0.09 mmol) for the HOAt. The resulting yellow oil (33.0. mg , 97% yield) was carried to the next step without further purification. MS 556.45 $(M+H)^+$.

[00563] *Part B: Ethyl 2-(2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazole-4-carboxamido)acetate, bistrifluoroacetic acid salt*: The product from **Example 39** Part A (33.0 mg, 0.06 mmol) was treated with TFA according the procedure described for **Example 1** Part B . The resulting residue was re-dissolved in MeOH/H_2O (9:1) containing 0.1% TFA and isolated by prep HPLC to yield 2.0 mg of the title compound(7%). ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.03 (m, 3 H), 1.27 (t, J = 7.15 Hz, 4 H), 1.37 (m, 3 H), 1.56 (m, 2 H), 1.72 (d, J = 13.20 Hz, 1 H), 1.83 (dd, J = 8.80, 3.85 Hz, 4 H), 2.20 (m, 1 H), 2.76 (d, J = 7.15 Hz, 3 H), 3.19 (dd, J = 13.75, 8.25 Hz, 1 H), 3.25 (m, 2H), 4.10 (s, 3 H), 4.20 (q, J = 7.15 Hz, 3 H), 5.25 (t, J=7.70 Hz, 1 H),

7.16 (t, J=7.15 Hz, 3 H), 7.19 (d, J=7.15 Hz, 1 H), 7.24 (t, J=7.15 Hz, 3 H), 7.67 (s, 1 H): HRMS $(M + Na)^+$ for $C_{24}H_{33}N_5O_4$, calcd m/z: 478.2403, obs: 478.2453.

Example 42

Methyl 2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylate, bistrifluoroacetic acid salt

[00564] *Part A: (S)-Methyl 2-(1-(tert-butoxycarbonyl)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylate*: To a solution of L-N-(Boc)-phenylalanine (265 mg, 1.0 mmole) and BOP reagent (464 mg, 1.0 mmole) in pyridine (10 mL) was added methyl 3,4-diaminobenzoate (166 mg, 1.0 mmole). The reaction mixture was stirred at 80 °C for 3 d. The solvent was removed under vacuum. The residue was re-dissolved in EtOAc. The solution was washed with water and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by prep HPLC to yield 178 mg of the amide (45%). MS 340.2 $(M+H)^+$.

[00565] *Part B: (S)-Methyl 2-(1-amino-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylate*: The product formed in **Example 42** Part A (178 mg, 0.45 mmol) was treated with TFA according to the procedure described for Example 1 Part B to yield 180 mg of the amine (76%). MS 296.2 $(M+H)^+$.

[00566] *Part C: Methyl 2-((S)-1-(trans-4-((tert-butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylate*: The product formed in **Example 42** Part B (178 mg, 0,34 mmol) was coupled with N-(Boc)-tranexamic acid according to the procedure described for **Example 2** Part A to yield 75 mg of the desired product (41 %). MS 535.5 $(M+H)^+$.

[00567] *Part D: Methyl 2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylate, bistrifluoroacetic acid salt*: The product formed in **Example 42** Part C (15 mg, 0.028 mmol) was treated with TFA according to the procedure described for **Example 2** Part B to yield 12 mg of the title compound (65 %). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H). 1.52-1.60 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.27-2.29 (m, 1H), 2.77, (d, J = 7.15 Hz, 2H), 3.45 (m, 2H), 3.96

(s, 3H), 5.48 (t, J = 8.25 Hz, 1H), 7.22-7.26 (m, 5H), 7.80 (d, J = 7.0 Hz, 1H), 8.19 (dd, J = 7.0 Hz, 1.2 Hz, 1H), 8.36 (s, 1H); MS 435.3 $(M+H)^+$.

Example 43

2-((S)-1-(*trans*-4-(Aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylic acid, bistrifluoroacetic acid salt

[00568] *Part A: 2-((S)-1-(trans-4-((tert-Butoxycarbonyl)methyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylic acid*: The compound from **Example 42** Part C (50 mg, 0.093 mmol) was hydrolyzed using conditions described for **Example 38** Part A with the exception that ethanol was used in place of methanol yielding 38 mg of the acid (78%). MS 521.3 $(M+H)^+$.

[00569] *Part B: 2-((S)-1-(trans-4-(Aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxylic acid, bistrifluoroacetic acid salt*: The compound from **Example 43** Part A (15 mg, 0.029 mmol) was converted to the title product using the procedure described for **Example 2** Part B (12 mg, 64 %). ^{1}H-NMR (400 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.27-2.28 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.43 (d, J = 8.34 Hz, 2H), 5.48 (t, J = 8.12 Hz, 1H), 7.22-7.26 (m, 5H), 7.80 (d, J = 8.78 Hz, 1H), 8.19 (dd, J = 8.35 Hz and 1.3 Hz , 1H), 8.36 (s, 1H); MS 421.2 $(M+H)^+$.

Example 44

2-((S)-1-(*trans*-4-(Aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxamide, bistrifluoroacetic acid salt

[00570] *Part A: tert-Butyl (trans-4-(((S)-1-(5-carbamoyl-1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate*: The compound from **Example 43** Part A (23 mg, 0.044 mmol) was subjected to the conditions described for **Example 1** Part C with the exception that ammonium hydroxide was used in place of 4-amidinobenzoic acid hydrochloride to provide 18 mg of the desired product (79 %). MS 520.0 $(M+H)^+$.

[00571] *Part B: 2-((S)-1-(trans-4-(Aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxamide, bistrifluoroacetic acid salt*: The compound from **Example 44** Part A (18 mg, 0.034 mmol) was reacted with TFA following the conditions described for **Example 2** Part B to yield 8 mg of the title compound (36%). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.27-2.28 (m, 1H), 2.77 (d, J = 7.14 Hz, 2H), 3.43 (d, J = 7.70 Hz, 2H), 5.48 (t, J = 8.24 Hz, 1H), 7.22-7.27 (m, 5H), 7.80 (d, J = 8.78 Hz, 1H), 8.05 (dd, J = 8.79 Hz, 1.64 Hz , 1H), 8.25 (s, 1H); MS 420.2 $(M+H)^+$.

Example 45

Ethyl 2-(2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazol-5-yl)acetate, bistrifluoroacetic acid salt

[00572] *Part A: Ethyl 2-(4-amino-3-nitrophenyl)acetate*: To a solution of 4-(aminophenyl)acetic acid ethyl ester (538 mg, 3.0 mmole) in acetic acid (20 mL) was added nitric acid (90%, 420 mg, 6 mmole). The reaction mixture was stirred at 100 °C for 4 h. The reaction was cooled to rt. Acetic acid was partially removed under vacuum. The residue was diluted with EtOAc. The pH of the solution was adjusted to 8-9 with 10% NaOH. It was washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The crude product was isolated by silica gel chromatography to give 128 mg (20% yield) of a bright yellow solid. It was taken into the next step without further purification.

[00573] *Part B: Ethyl 2-(3,4-diaminophenyl)acetate*: To a suspension of 10% palladium on carbon (15 mg) in 2 mL of MeOH was added a solution of the product from **Example 45** Part A (128 mg) in MeOH (8 mL). The reaction mixture was stirred under one atmosphere of hydrogen at rt for 4 h. The catalyst was filtered. To the filtrate was added 1 N HCl (0.1 mL) and the solvent was evaporated to dryness to yield 130 mg the crude product as the HCl salt (86% yield). MS 195.2 $(M+H)^+$.

[00574] *Part C: (S)-Ethyl 2-(2-(1-(tert-butoxycarbonyl)-2-phenylethyl)-1H-benzo[d]imidazol-5-yl)acetate*: The product from **Example 45** Part B (130 mg, 0.49 mmol) and L-N-(Boc)-phenylalanine (130 mg, 0.49 mmol) were subjected to the

conditions described for Example 42 Part A to yield 210 mg (100% yield) of the desired product. MS 424.3 $(M+H)^+$.

[00575] *Part D: Ethyl 2-(2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazol-5-yl)acetate, bistrifluoroacetic acid salt*: The product from Example 45 Part C was treated with TFA and then coupled with N-(Boc)-tranexamic acid according to the procedures described for Example 2 Part A to yield the desired product which was reacted with TFA following the conditions described for Example 2 Part B to yield the title compound. MS 463.43 (M+H)+. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.24 (t, J = 3.30 Hz, 3 H), 1.35 (m, 2H), 1.56 (m, 1H), 1.78 (br d, J = 12.65 Hz, 1H), 1.86 (m, 3H), 2.28 (m, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.31 (s, 2H), 3.42 (d, J = 7.70 Hz, 2 H), 3.84 (s, 2 H), 4.16 (q, J = 7.15 Hz, 2H), 5.46 (t, J = 8.25 Hz, 1 H), 7.23 (m, 5 H), 7.51 (d, J = 8.80 Hz, 1H), 7.68 (d, J = 8.80 Hz, 2H); MS 463.4 $(M+H)^+$.

Example 46

2-(2-((S)-1-(*trans*-4-(Aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazol-5-yl)acetic acid, bistrifluoroacetic acid salt

[00576] The product from Example 45 Part D was hydrolyzed with LiOH and then treated with TFA following the conditions described for Example 2 Part B to yield the title compound. MS 435.4 $(M+H)^+$. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.35 (m, 2H), 1.55 (m, 1H), 1.78 (br d, J = 12.10 Hz, 1H), 1.86 (m, 3H), 2.28 (m, 1H), 2.77 (d, J = 6.60 Hz, 2H), 3.31 (s, 2H), 3.42 (d, J = 8.25 Hz, 2 H), 3.82 (s, 2 H), 5.46 (t, J = 8.25 Hz, 1 H), 7.23 (m, 5 H), 7.52 (d, J = 8.24 Hz, 1H), 7.67 (d, J = 8.25 Hz, 2H); MS 435.4 $(M+H)^+$.

Example 47

***trans*-N-((S)-1-(5-(2-amino-2-oxoethyl)-1H-benzo[d]imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt**

[00577] This compound was prepared from the product from Example 45 Part D using the same procedures described for the synthesis of Example 44. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.06 (m, 2H), 1.35 (m, 2H), 1.55 (m, 1H), 1.78 (br d, J =

11.86 Hz, 1H), 1.86 (m, 3H), 2.28 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.31 (s, 2H), 3.42 (d, J = 8.35 Hz, 2 H), 3.70 (s, 2 H), 5.46 (t, J = 8.35 Hz, 1 H), 7.23 (m, 5 H), 7.52 (d, J = 8.35 Hz, 1H), 7.67 (d, J = 8.325 Hz, 2H); MS 434.3 $(M+H)^+$.

Example 48

***trans*-4-(Aminomethyl)-N-((S)-2-phenyl-1-(5-phenyloxazol-2-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt**

[00578] *Part A: (S)-2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-(2-oxo-2-phenyl-ethyl)-3-phenyl-propionamide*: N-Phthaloyl-L-phenylalanine (290 mg, 1 mmol) and 2-aminoacetophenone (171 mg, 1 mmol) were dissolved in 10 mL of pyridine. Bop reagent (470 mg, 1.1 mmol) was added The mixture was stirred at rt under N_2 for 12 h. The solvent was removed. The residue was dissolved in EtOAc and washed with water and sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 412 mg of the product (100% yield). MS 413.2 $(M+H)^+$.

[00579] *Part B: (S)-2-(2-Phenyl-1-(5-phenyloxazol-2-yl)ethyl)isoindoline-1,3-dione*: The product from **Example 48** Part A (412 mg, 1 mmol) was dissolved in DMF and treated with phosphorous oxychloride (460 mg, 3 mmol) at 90 °C according to the procedure described by Robert Dow et al. (J. Org. Chem., 1990, *55*, 386) to yield 160 mg (41% yield) of the product. MS 395.2 $(M+H)^+$.

[00580] *Part C: (S)-2-Phenyl-1-(5-phenyloxazol-2-yl)ethanamine*: A solution of the product from **Example 48** Part B (160mg, 0.4 mmol) in EtOH (10mL) was added to hydrazine (39 mg, 1.2 mmol). The reaction mixture was refluxed for 2 h. It was cooled to rt. EtOH was removed under vacuum. The residue was re-dissolved in dichloromethane. The undissolved solid was removed by filtration. The filtrate was concentrated to yield 95 mg of the product as a yellow solid (90% yield). MS 265.1 $(M+H)^+$.

[00581] *Part D: trans-4-(Aminomethyl)-N-((S)-2-phenyl-1-(5-phenyloxazol-2-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt*: The product from **Example 48** Part C (95 mg, 0.35 mmol) was converted to the title compound by sequential application of the procedures described for **Example 2** Part A and Part B

(26%). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.22 (m, 1H), 2.77 (d, J = 7.14 Hz, 2H), 3.20 (m, 1H), 3.33 (m, 1H), 5.41 (m, 1H), 7.22-7.27 (m, 5H), 7.34 (t, J = 7.15 Hz, 1H), 7.42 (m, 3H), 7.63- 7.65 (d, J = 8.25Hz, 2H); MS 404.3 $(M+H)^+$.

Example 49

***trans*-4-(Aminomethyl)-N-((S)-2-phenyl-1-(5-phenyl-2H-1,2,4-triazol-3-yl)ethyl)cyclohexane-carboxamide, bistrifluoroacetic acid salt**

[00582] *Part A: (S)-tert-Butyl 2-phenyl-1-(5-phenyl-2H-1,2,4-triazol-3-yl)ethylcarbamate*: L-N-(Boc)-phenylalanine (265 mg, 1 mmole) and hydrazine (64 mg, 2 mmol) were combined using the conditions described for **Example 1** Part C to form 279 mg of hydrazoic acid (100% yield). MS 280.1 $(M+H)^+$. To a solution of hydrazoic acid (279 mg, 1.0 mmole) and Et_3N (161 mg, 1.6 mmole) in 10 mL of acetonitrile was added ethylbenzimidate hydrochloride (278 mg, 1.5mmole). The reaction was heated to reflux for 24 h. The reaction was cooled to rt and diluted with EtOAc. The mixture was washed with water and brine, dried over Na_2SO_4, filtered and evaporated to dryness in *vacuo*. The crude product was purified by prep HPLC to yield 154 mg of an oil (42% yield). MS 365.2 $(M+H)^+$.

[00583] *Part B: trans-4-(Aminomethyl)-N-((S)-2-phenyl-1-(5-phenyl-2H-1,2,4-triazol-3-yl)ethyl)cyclohexane-carboxamide, bistrifluoroacetic acid salt*: The product from **Example 49** Part A (154 mg, 0.42 mmol) was converted to the title compound by sequential application of the procedures described for **Example 1** Part B, **Example 2** Part A and Part B (28%). ^{1}H-NMR (400 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.21 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.18-3.21 (m,1H), 3.31 (m, 1H), 5.42 (t, J = 8.12 Hz, 1H), 7.22-7.26 (m, 5H), 7.51-7.52 (m ,3H), 7.96-7.98 (m, 2H); MS 404.2 $(M+H)^+$.

Example 50 ***trans*-4-(Aminomethyl)-N-((S)-2-phenyl-1-(3-phenyl-1H-pyrazol-5-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt**

[00584] *Part A: 3-Oxo-3-phenylpropanoic acid*: To a solution of ethyl benzoyl acetate (2.88g, 15 mmol) in EtOH (30 mL) was added 1N NaOH (30 mL). The reaction mixture was stirred at rt for 72 h. It was cooled to 0 °C and acidified with 1N HCl . EtOH was removed under reduced pressure. The aqueous layer was extracted twice with dichloromethane. The combined dichloromethane solution was washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give a light yellow solid. (600 mg, 24%). MS 165.1 $(M+H)^+$.

[00585] *Part B: (S)-Benzyl 3,5-dioxo-1,5-diphenylpentan-2-yl carbamate*: To a solution of the product from **Example 50** Part A (600mg, 3.65 mmol) in THF (20 mL) and MeOH (20 mL) was added magnesium ethoxide (417mg, 3.65 mmol). The mixture was stirred at r.t. for 4 h. The solvents were removed under reduced pressure. The crude product was dissolved in DMF (2 mL) and added to a mixture of N-CBZ-L-phenylalanine (800mg, 2.68mmol), 1,1'-carbonyldiimidazole (520mg, 3.21mmol) in DMF (4 mL) which had been stirred for 2 h at rt. The resulting mixture was stirred at rt overnight. It was diluted with EtOAc, washed with diluted HCl, water and brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by prep HPLC to give the product (140 mg, 13%). MS 402.1 $(M+H)^+$.

[00586] *Part C: ((S)-Benzyl 2-phenyl-1-(3-phenyl-1H-pyrazol-5-yl)ethylcarbamate*: To a solution of **Example 50** part B (32mg, 0.08mmol) in EtOH (3mL) was added hydrazine hydrate (3 mg, 0.09 mmol). The reaction mixture was heated at 60 °C for 3 h. EtOH was removed *in vacuo* to give the desired product (0.32 mg, 100%). MS 398.1 $(M+H)^+$.

[00587] *Part D: (S)-2-Phenyl-1-(3-phenyl-1H-pyrazol-5-yl)ethanamine*: To a solution from **Example 50** Part C in MeOH (3 mL) was added 10% Pd/ C (5 mg). The reaction mixture was stirred under H_2 at rt for 4 h. The catalyst was removed by filtration. The crude mixture was purified by prep HPLC to give the desired product (12mg, 57%). MS 262.2 $(M-H)^-$.

[00588] *Part E: trans-4-(Aminomethyl)-N-((S)-2-phenyl-1-(3-phenyl-1H-pyrazol-5-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt*: The product from **Example 50** Part D (12 mg, 0.046 mmol) was converted to the title compound by sequential application of the procedures described for **Example 2** Part A and Part B (11 mg, 46%). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.30-1.33 (m,

1H),1.43-1.46 (m, 1H), 1.56 (m, 1H), 1.64 (m, 1H), 1.83 (m, 3H), 2.16-2.18 (m, 1H), 2.75 (d, J = 7.03 Hz, 2H), 3.08-3.10 (m,1H), 3.27 (m, 1H), 5.35 (t, J = 8.12 Hz, 1H), 6.61 (s, 1H), 7.22 (m, 1H), 7.23 (m , 4H), 7.35-7.36 (t, J = 7.15Hz, 1H), 7.41-7.44 (t, J = 7.70Hz, 2H), 7.69-7.71 (d, J = 7.15Hz, 2H); MS 403.1 $(M+H)^+$.

Example 51

***trans*-4-(aminomethyl)-N-((S)-1-(5-oxo-1-phenyl-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenylethyl)-cyclohexanecarboxamide, bistrifluoroacetic acid salt**

[00589] *Part A: (S)-Benzyl 1-(5-oxo-1-phenyl-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate*: A solution of (S)-N-CBZ-phenylalanine nitrile (140 mg, 0.5 mmol) and sodium methoxide (13 mg, 0.24 mmol) in MeOH (4mL) was stirred at 30 °C for 3 h. Acetic acid (1mg, 0.2mmol) was added, followed by phenyl hydrazine (108 mg, 1 mmol). The reaction mixture was stirred at rt for 18 h. The mixture was cooled to 0 °C, and the solid was removed by filtration. The MeOH solution was purified by silica gel chromatography to give a yellow oil, which was dissolved in THF (6 mL) and 1,1'-carbonyldiimidazole (68 mg, 0.42 mmole) was added. The mixture was heated to reflux for 48 h. The reaction was cooled to rt, diluted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give 38 mg (66%) of the product as a red solid. MS 413.2 $(M-H)^-$.

[00590] *Part B: Trans-4-(aminomethyl)-N-((S)-1-(5-oxo-1-phenyl-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-phenylethyl)-cyclohexanecarboxamide, bistrifluoroacetic acid salt*: The product of **Example 51** Part A (38 mg, 0.09 mmol) was converted to the title compound by sequential application of the procedures described for **Example 50** Part D, and **Example 2** Part A and Part B (8 mg,17%). ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.30-1.33 (m, 1H), 1.43-1.46 (m, 1H), 1.56 (m, 1H), 1.67 (m, 1H), 1.81- 1.86 (m, 3H), 2.16-2.18 (m, 1H), 2.75 (d, J = 7.15 Hz, 2H), 3.08-3.10 (m,1H), 3.31 (m, 1H), 5.15-5.17 (m, 1H), 7.19-7.21 (m, 2H), 7.27-7.28 (m, 4H), 7.40-7.43 (t, J = 7.97Hz, 2H), 7.85-7.87 (d, J = 7.69Hz, 2H); MS 420.1 $(M+H)^+$.

Example 52

***trans*-4-(aminomethyl)-N-((S)-2-phenyl-1-(2-phenyl-1H-imidazol-4-yl)ethyl)cyclohexane-carboxamide, bistrifluoroacetic acid salt**

[00591] *Part A: (S)-Benzyl 2-phenyl-1-(2-phenyl-1H-imidazol-4-yl)ethylcarbamate*: A solution of (S)-benzyl-4-bromo-3-oxo-1-phenylbutan-2-yl carbamate (376 mg, 1.0 mmole) and sodium formate (68 mg, 1.0 mmole) in EtOH (15 mL) was heated to reflux for 14 h. Benzamidine (240 mg, 1.5 mmole) and sodium bicarbonate (400 mg, 4.7 mmole) were added to the reaction. The reaction mixture was heated to refluxed for an additional 24 h. The reaction was cooled to rt and the dried in *vacuo*. The residue was re-dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by silica gel chromatography to yield 33 mg (8% yield). MS 398.1 $(M+H)^+$.

[00592] Part B: *Trans-4-(aminomethyl)-N-((S)-2-phenyl-1-(2-phenyl-1H-imidazol-4-yl)ethyl)cyclohexane-carboxamide, bistrifluoroacetic acid salt*: The product from **Example 52** Part A (33 mg, 0.083 mmol) was converted to the title compound by sequential application of the procedures described for **Example 50** Part D, and **Example 2** Part A and Part B (5 mg,12% yield). ^{1}H-NMR (400 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.30-1.33 (m, 1H), 1.43-1.46 (m, 1H), 1.56 (m, 1H), 1.67 (m, 1H), 1.83 (m, 3H), 2.16-2.18 (m, 1H), 2.75 (d, J = 7.03 Hz, 2H), 3.08-3.10 (m,1H), 3.31 (m, 1H), 5.34-5.36 (m, 1H), 7.22-7.29 (m, 5H), 7.51 (s, 1H), 7.62-7.68 (m, 3H), 7.87-7.89 (m, 2H); MS 403.3 $(M+H)^+$.

Example 53

N-(4-Carbamimidoylphenyl)-3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanamide, Bis-trifluoroacetic acid salt

[00593] *Part A: 2-Benzyl-3-methoxy-3-oxopropanoic acid*: Benzyl malonic acid (19.4 g, 0.10 mol) was dissolved in 180 mL of MeOH. The mixture was cooled in an ice-bath and to it was added thionyl chloride dropwise over 30 min (7.3 mL, 0.10 mol). The mixture was stirred in the ice-bath for 30 min and then at RT for 30 min under N_2. The solvent was removed, and the residue was dissolved in aqueous

$NaHCO_3$. The basic solution was extracted with EtOAc to remove the bis-ester which was discarded. The aqueous solution was then acidified with aqueous HCl to pH 5 and extracted with EtOAc. The EtOAc extract was washed with brine, dried over Na_2SO_4, and concentrated to give 7.2 g of 2-benzyl-3-methoxy-3-oxopropanoic acid (35%). MS 209.24 $(M+H)^+$.

[00594] *Part B: Methyl 3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanoate*: The product from Example 53 Part A (1.04 g, 5.0 mmol) was dissolved in EtOH (13 mL) and a solution of Cs_2CO_3 (0.81 g, 2.5 mmol) in H_2O (13 mL) was added. The reaction mixture was stirred at RT for 1 h under N_2. The solvent was removed under vacuum, and the resulting salt was suspended in DMF (20 mL). 2-Bromoacetophenone (1.3 g, 6.6 mmol) was added in a single portion, and the reaction stirred at RT under N_2 for 2 h. The reaction was filtered to remove CsBr. The solids were washed with DMF. The combined washings and filtrate were concentrated in *vacuo* to yield a yellow solid. The crude intermediate was placed in a flask fitted with a Dean-Stark trap and dissolved in xylene (40 mL). NH_4OAc (7.78 g, 100 mmol) was added to the flask and the reaction was heated to reflux for 3 h. The reaction was cooled to RT and the solvent removed in *vacuo*. The residue was redissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel, EtOAc/ hexane) to yield 600 mg of the desired product (39%). MS 307.29 $(M+H)^+$.

[00595] *Part C: 3-Phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanoic acid*: The product from Example 53 Part B (350 mg, 1.14 mmol) was dissolved in 9 mL of EtOH and 1N NaOH (3 mL) was added. The mixture was stirred at RT under N_2 for 30 min. Aqueous HCl was added to the reaction mixture until pH 5. The precipate formed was filtered and dried to afford 284 mg of the desired product (85%). MS 293.33 $(M+H)^+$.

[00596] *Part D:N-(4-Carbamimidoylphenyl)-3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanamide bis-TFA salt*: The product from Example 53 from Part C (40 mg, 0.14 mmol) and 4-amidinobenzamidine hydrochloride (48 mg, 0.16 mmol) were dissolved in anhydrous pyridine (2 mL). BOP reagent (90 mg, 0.16 mmol) was added and the reaction was stirred at RT under N_2 for 48 h. The solvent was removed in *vacuo*. The residue was redissolved in CH_3OH/H_2O (9:1) containing 0.1% TFA,

and purified by reverse phase HPLC (C18, 28x100 mm, MeOH/H_2O/0.1%TFA gradient) to yield 15 mg of the title compound (17% yield). ^{1}H-NMR (400 MHz, d_4-MeOH) δ 3.33 (dd, J = 13.40, 9.45 Hz, 1 H), 3.52 (dd, J = 13.62, 7.03 Hz, 1 H), 4.54 (dd, J = 9.23, 7.03 Hz, 1 H), 7.12 (m, 5 H), 7.39 (m, 3 H), 7.57 (d, J = 6.59 Hz, 2 H), 7.70 (m, 3 H), 7.76 (m, 2 H). HRMS $(M + H)^+$ for $C_{25}H_{24}N_5O$, calcd m/z: 410.1981, obs: 410.2001.

Example 54

N-(3-Carbamimidoylphenyl)-3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanamide, Bis-trifluoroacetic acid salt

[00597] The title compound was prepared using the same procedures described for Example 53. NMR (400 MHz, d_4-MeOH) δ 3.42 (dd, J = 13.62, 9.23 Hz, 1 H), 3.61 (dd, J = 13.62, 7.03 Hz, 1 H), 4.61 (dd, J = 9.01, 7.25 Hz, 1 H), 7.24 (m, 5 H), 7.51 (m, 5 H), 7.66 (d, J = 7.91 Hz, 2 H), 7.77 (m, 2 H), 8.19 (s, 1 H); MS 410.20, $(M+H)^+$.

Example 55

***trans*-N-(4-(Aminomethyl)cyclohexyl)-3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanamide, bistrifluoroacetic acid salt**

[00598] *Part A: Benzyl (trans-4-aminocyclohexyl)methylcarbamate*: t-Butyl *trans*-4-aminomethylcyclohexylcarbamate (344 mg, 1.5 mmol) was dissolved in CH_2Cl_2 (7 mL) and cooled in an ice-bath. Triethylamine (0.21 mL, 1.5 mmol) was added, followed by benzyl chloroformate (0.22 mL, 1.5 mmol) dropwise. The mixture was stirred at rt under N_2 for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water and brine, dried over Na_2SO_4, filtered, and concentrated to a white solid. This solid was dissolved in 10 mL of 4 N HCl-dioxane and stirred at rt for 10 min. The solvent was removed. The residue was dried under vacuum to give 350 mg of the desired product as a white solid (78%). MS 263.36 $(M+H)^+$.

[00599] *Part B: Benzyl (trans-4-(3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanamido)cyclohexyl)methylcarbamate*: The product from Example 55 Part A

(75 mg, 0.25 mmol) and the product from **Example 53** Part C (60 mg, 0.21 mmol) were dissolved in anhydrous pyridine (5 mL). BOP reagent (115 mg, 0.26 mmol) was added and the reaction was stirred at RT under N_2 for 4 h. The solvent was removed in *vacuo*. The residue was re-dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexane) to yield 50 mg of the desired product (44%). MS 537.32 $(M+H)^+$.

[00600] *Part C: N-(trans-4-(aminomethyl)cyclohexyl)-3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanamide, Bis-trifluoroacetic acid salt*: The product from **Example 55** Part B (50 mg, 0.093 mmol) was dissolved in MeOH (8 mL) and a catalytic amount of 10% Pd/C was added. The mixture was placed under 1 atm of H_2 for 4 h. It was filtered through celite and washed with MeOH. The filtrate was concentrated and purified by reverse phase HPLC to give 33 mg of the title compound (56%). ^{1}H-NMR (400 MHz, d_4-MeOH) δ 0.92-1.22 (m, 4 H), 1.59 (m, 1 H), 1.70-1.88 (m, 4 H), 2.69 (m, 2 H), 3.21 (m, 1 H), 3.35 (m, 1 H), 3.50 (m, 1 H), 4.32 (t, J = 8.35 Hz, 1 H), 7.12-7.32 (m, 5 H), 7.38-7.54 (m, 3 H), 7.66 (d, J = 7.03 Hz, 2 H), 7.75 (s, 1 H). MS 403.39 $(M+H)^+$.

Example 56

4-(2-(1-(4-Carbamimidoylphenylamino)-1-oxo-3-phenylpropan-2-yl)-1H-imidazol-4-yl)benzamide, bis-trifluoroacetic acid salt

[00601] *Part A: Methyl 2-(4-(4-cyanophenyl)-1H-imidazol-2-yl)-3-phenylpropanoate*: 2-Benzyl-3-methoxy-3-oxopropanoic acid from **Example 53** Part A (5.0 g, 24.0 mmol) was dissolved in EtOH (40 mL) and a solution of Cs_2CO_3 (4.0 g, 12.0 mmol) in H_2O (40 mL) was added. The reaction mixture was stirred at rt for 1 h under N_2. The solvent was removed under vacuum and the resulting salt was suspended in DMF (85 mL). 4-(2-bromoacetyl)benzonitrile (5.4 g, 24.0 mmol) was added in a single portion and the reaction stirred at rt under N_2 for 4 h. The reaction was filtered to remove CsBr. The solids were washed with DMF. The combined washings and filtrate were concentrated in *vacuos* to yield a yellow solid. The crude intermediate was placed in a flask fitted with a Dean-Stark trap and dissolved in xylene (200 mL). NH_4OAc (38.9 g, 500 mmol) was added to the flask and the

reaction was heated to reflux for 3 h. The reaction was cooled to rt and the solvent removed *in vacuo*. The residue was redissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel, EtOAc/ hexane) to yield 2.4 g of desired product (30%). MS 332.27 $(M+H)^+$.

[00602] *Part B: 2-(4-(4-carbamoylphenyl)-1H-imidazol-2-yl)-3-phenylpropanoic acid*: The product from **Example 56** Part A (0.99 g, 3.0 mmol) was dissolved in 10 mL of DMSO. Potassium carbonate (1.24 g, 9.0 mmol) was added. The mixture was cooled to 0-5 °C and 30% H_2O_2 (3.18 mL of 30% aqueous solution) was added, followed by magnesium oxide (0.24 g, 15 mmol). The cooling bath was removed and the mixture was stirred at RT under N_2 for 4 h. The mixture was filtered to remove inorganic material. Water (30 mL) was added to the filtrate and the resulting mixture was stirred at rt for 40 min. The mixture was acidified with 1N HCl to pH 5. The precipitate formed was filtered and dried to afford 0.67 g of the acid (67%). MS 336.30 $(M+H)^+$.

[00603] *Part C: 4-(2-(1-(4-Carbamimidoylphenylamino)-1-oxo-3-phenylpropan-2-yl)-1H-imidazol-4-yl)benzamide, bis-trifluoroacetic acid salt*: The acid from **Example 56** Part B (55 mg, 0.16 mmol) and 4-amidinobenzamidine hydrochloride (58 mg, 0.34 mmol) were dissolved in anhydrous pyridine (3 mL). BOP reagent (108 mg, 0.24 mmol) was added and the reaction was stirred at RT under N_2 for 48 h. The solvent was removed in *vacuo*. The residue was redissolved in CH_3OH/H_2O (9:1) containing 0.1% TFA, and purified by reverse phase HPLC ($MeOH/H_2O$/0.1%TFA gradient) to yield 11 mg of the title compound (10%). ^{1}H-NMR (400 MHz, d_4-MeOH) δ 3.34 (m, 1 H), 3.49 (m, 1 H), 4.29 (t, J = 7.91 Hz, 1 H), 7.17 (m, 1 H), 7.22 (m, 4 H), 7.56 (s, 1 H), 7.78 (m, 6 H), 7.89 (m, 2 H). HRMS $(M + H)^+$ for $C_{26}H_{25}N_6O_2$, calcd m/z: 453.2039, obs: 453.2025.

Example 57

4-(2-(1-(1-Aminoisoquinolin-6-ylamino)-1-oxo-3-phenylpropan-2-yl)-1H-imidazol-4-yl)benzamide, bis-trifluoroacetic acid salt

[00604] 2-(4-(4-Carbamoylphenyl)-1H-imidazol-2-yl)-3-phenylpropanoic acid from **Example 56** Part B (36 mg, 0.11 mmol) and tert-butyl 6-aminoisoquinolin-1-

ylcarbamate (18 mg, 0.050 mmol) were dissolved in anhydrous pyridine (3 mL). BOP reagent (50 mg, 0.11 mmol) was added and the reaction was stirred at 60 °C under N_2 for 3 h and then at rt for 48 h. The solvent was removed in *vacuo*. The residue was redissolved in EtOAc (1 mL) and 4N HCl-dioxane (1 mL) and stirred at rt for 1.5 h. The mixture was concentrated and then re-dissolved in CH_3OH/H_2O (9:1) containing 0.1% TFA, and purified by reverse phase HPLC ($MeOH/H_2O$/0.1%TFA gradient) to yield 6.0 mg of the title compound (17%). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 3.45 (m, 1 H), 3.63 (m, 1 H), 4.62 (dd, J = 7.03 Hz, 1 H), 7.14 (d, J = 7.03 Hz, 1 H), 7.26 (m, 5 H), 7.53 (d, J = 7.03 Hz, 1 H), 7.79 (d, J = 8.35 Hz, 2H), 7.85 (dd, J = 9.23, 2.20 Hz, 1H), 7.90 (s, 1 H), 7.99 (d, J = 8.35 Hz, 2H), 8.33 (d, J = 1.76 Hz, 1H), 8.38 (d, J = 8.79 Hz, 1H). MS 477.3 $(M + H)^+$.

Example 58

4-(2-(1-(Isoquinolin-6-ylamino)-1-oxo-3-phenylpropan-2-yl)-1H-imidazol-4-yl)benzamide, bis-trifluoroacetic acid salt

[00605] The title compound was prepared using the same methods described in Example 57. MS 462.19 $(M + H)^+$. ^{1}H- NMR (400 MHz, MeOH-d_4) δ 3.36 (d, J = 7.47 Hz,1 H), 3. 51 (d, J = 8.35 Hz,1 H), 4.31 (t, J = 7.91 Hz, 1 H), 7.15 (m, 1 H), 7.23 (d, J = 6.59 Hz, 4H), 7.54 (s, 1 H), 7.65 (dd, J = 8.79, 2.20 Hz, 2H), 7.74 (d, J = 6.15 Hz, 1H), 7.80 (d, J = 8.79 Hz, 2 H), 7.89 (m, 2H), 8.03 (d, J = 9.23 Hz, 1H), 8.35 (m, 1H), 9.10 (s, 1 H).

Example 59

4-(2-(4-(4-carbamimidoylphenyl)-1H-imidazol-2-yl)-3-phenylpropanamido)benzamide, bis-trifluoroacetic acid salt

[00606] *Part A: 2-(4-(4-Cyanophenyl)-1H-imidazol-2-yl)-3-phenylpropanoic acid*: Methyl 2-(4-(4-cyanophenyl)-1H-imidazol-2-yl)-3-phenylpropanoate from Example 56 Part A (60 mg, 0.20 mmol) was dissolved in 4 mL of EtOH. NaOH (1.5 mL of 1N aqueous solution) was added and the mixture was stirred RT for 1.5 h. The mixture was acidified with 1N HCl to pH 5. The precipitate formed was filtered and dried to give 40 mg of the acid (63%). MS 318.3 $(M+H)^+$.

[00607] *Part B: 4-(2-(4-(4-Cyanophenyl)-1H-imidazol-2-yl)-3-phenylpropanamido)benzamide*: The acid from Example 59 Part A (100 mg, 0.32 mmol), triethylamine (150 µL, 1.2 mmol), and BOP reagent (210 mg, 0.48 mmol) were dissolved in THF (9 mL). The mixture was stirred at rt for 15 min and 4-aminobenzamide (47 mg, 0.35 mmol) was added. The resulting mixture was heated at 70 °C under N_2 for 1 h. The mixture was concentrated and then re-dissolved in EtOAc. It was washed with water and brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane) to give 45 mg of the desired product (32%). MS 436.3 $(M+H)^+$.

[00608] *Part C: 4-(2-(4-(4-Carbamimidoylphenyl)-1H-imidazol-2-yl)-3-phenylpropanamido)benzamide, bis-trifluoroacetic acid salt*: Hydroxylamine hydrochloride (72 mg, 1.0 mmol) was dissolved in DMSO (1 mL) and triethylamine (0.14 mL, 10 eq) was added. The mixture was stirred for 5 min and the precipitate was filtered off. The filtrate was added to the product from Example 59 Part B (28 mg, 0.064 mmol) and the mixture was stirred at rt for 15 min, then 4-aminobenzamide (47 mg, 0.35 mmol) was added. The resulting mixture was heated at 65 °C under N_2 for 1.5 h. It was cooled and water was added. The precipitate formed was filtered and dried. The solid was then dissolved in CH_2Cl_2 (3 mL) and acetic anhydride (13 µL) was added. The mixture was stirred at rt under N_2 for 1.5 h. The CH_2Cl_2 was removed and the residue was dissolved in MeOH-HOAc (3 mL of 10:1 solution). Pd/C (10%, 18 mg) was added and the mixture was placed under a balloon of hydrogen for 3 h. It was filtered through Celite, concentrated, then re-dissolved in CH_3OH/H_2O (9:1) containing 0.1% TFA, and purified by reverse HPLC (MeOH/H_2O/0.1%TFA gradient) to yield 8.0 mg of the title compound (18%). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 3.37 (m, 1H), 3.45 (m, 1 H), 4.24 (t, J = 7.91 Hz, 1 H), 7.16 (m, 1 H), 7.22 (m, 4 H), 7.62 (d, J = 8.79 Hz, 3 H), 7.80 (m, 4 H), 7.94 (d, J = 8.79, 2 H). MS 453.4 $(M + H)^+$.

Example 60

4-(2-(1-(4-Carbamimidoylbenzylamino)-1-oxo-3-phenylpropan-2-yl)-1H-imidazol-4-yl)benzamide, bis-trifluoroacetic acid salt

[00609] The acid from Example 56 Part B was coupled with 4-cyanobenzylamine following the procedure of Example 59 Part B. The cyano group was then converted to the corresponding benzamidine using the procedures of Example 59 Part C. MS 467.22 $(M+H)^+$. ^{1}H-NMR (400 MHz, MeOH-d_4) δ 3.37 (dd, J = 13.62, 8.35 Hz, 1H), 3.53 (m, 1 H), 4.37 (d, J= 15.82 Hz, 1 H), 4.55 (m, 2 H), 7.22 (m, 2 H), 7.29 (m, 5 H), 7.71 (d, J= 8.35 Hz, 2 H), 7.79 (d, J= 8.79 Hz, 2 H), 7.91 (s, 1 H), 7.99 (d, J = 8.35 Hz, 2 H).

Example 61

N-(4-Carbamimidoylphenyl)-4-phenyl-3-(4-phenyl-1H-imidazol-2-yl)butanamide, Bis-trifluoroacetic acid salt

[00610] This compound was prepared following the same procedures described in Example 53 using 2-benzylsuccinic acid as the starting material. MS 424.21 $(M+H)^+$. ^{1}H-NMR (400 MHz, MeOH-d_4) δ 3.107 (d, J = 3.95 Hz, 1H), 3.15 (m, 1 H), 3.25 (dd, J= 13.40, 6.37 Hz, 1 H), 3.95 (m, 1 H), 7.12 (d, J = 6.95 Hz, 2 H), 7.25 (m, 3 H), 7.46 (m, 3 H), 7.61 (d, J= 7.03 Hz, 2 H), 7.69 (s, 1 H), 7.75 (m, 4 H).

Example 62

4-(Aminomethyl)-N-((S)-1-(4-(3-methoxyphenyl)-1H-imidazol-2-yl)-2-phenylethyl)cyclohexane-carboxamide, bistrifluoroacetic acid salt

[00611] *Part A: (S)-tert-Butyl 1-(1H-imidazol-2-yl)-2-phenylethylcarbamate*: (*S*)-Tert-butyl 1-oxo-3-phenylpropan-2-yl carbamate (5.08 g, 20.4 mmol) and glyoxal trimeric dihydrate (2.2 g, 10.1 mmol) were dissolved in anhydrous MeOH (30 mL). Ammonia in methanol (2.0 M, 45.6 mL, 92.4 mmol) was added and the reaction was stirred for 48 h at rt. The solvent was removed under vacuum. The resulting oil was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and evaporated in *vacuo* to yield 1.4 g (47%) of white solid. MS 288.15 $(M+H)^+$.

[00612] *Part B: (S)-tert-Butyl 1-(4,5-dibromo-1H-imidazol-2-yl)-2-phenylethylcarbamate*: The product from Example 62 Part A (510 mg, 1.8 mmol) was dissolved in chloroform (10 mL) and treated with NBS (600 mg, 3.38 mmol) at rt. The reaction was stirred for 1 h. The solvent was removed under vacuum and the

crude product purified using silica gel chromatography to yield 510 mg (64%) of a white solid. MS 445.91 $(M+H)^+$.

[00613] *Part C: (S)-tert-Butyl 1-(4-bromo-1H-imidazol-2-yl)-2-phenylethylcarbamate*: The product from **Example 62** Part B (821 mg, 2.38 mmol) was dissolved in mixture of 1,4 dioxanes (8 ml) and water (2 mL). Sodium sulfite (3.00g, 23.8 mmol) and tetrabutylammonium hydrogensulfate (2.01 g, 5.95 mmol) were added. The reaction was heated at 100° C for 48 h. The reaction was diluted with EtOAc and the solids were filtered off. The filtrate was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by silica gel chromatography to provide 200 mg (24%) of a white solid. MS 366.3 $(M+H)^+$.

[00614] *Part D: (S)-1-(4-bromo-1H-imidazol-2-yl)-2-phenylethanamine*: The product from **Example 62** Part C (560 mg, 1.53 mmol) was treated with TFA according to the procedure described for **Example 1** Part B to provide 490 mg of the crude product as a yellow oil that contained excess TFA. The crude product was used in the next reaction without further purification. MS 268.3 $(M+H)^+$.

[00615] *Part E: tert-Butyl ((1S,4r)-4-(((S)-1-(4-bromo-1H-imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate*: The product from **Example 62** Part D (494 mg, 1.86 mmol) and N-Boc-tranexamic acid (480 mg, 1.8 mmol) were treated using the conditions described in **Example 2** Part A. The resulting white solid(780 mg, 83 %) was carried to the next step without further purification. MS 503.28 $(M+H)^+$.

[00616] *Part F: tert-Butyl ((1S,4r)-4-(((S)-1-(4-(3-methoxyphenyl)-1H-imidazol-2-yl)-2-phenylethyl)carbamoyl)cyclohexyl)methylcarbamate*: The product from **Example 62** Part E (30.0 mg, 0.059 mmol) was weighed into a vial containing 3-methoxyphenyl boronic acid (11 mg, 0.07 mmol) and K_3PO_4 (38 mg, 0.177 mmol). The solids were dissolved in 1,4 dioxanes (0.5 mL). Palladium (I) tri tert-butyl phosphine bromide dimer (19 mg , 0.024 mmol) was added, and the vial was sealed under argon. The reaction was heated using microwave irradiation at 110° C for 1 hr. The reaction was cooled to rt, and the solids filtered off. The filtrate was collected and dried under vacuum. The crude product, contaminated with starting material, was carried forward to next step. MS 433.22 $(M+H)^+$.

[00617] *Part G: 4-(Aminomethyl)-N-((S)-1-(4-(3-methoxyphenyl)-1H-imidazol-2-yl)-2-phenylethyl)cyclohexane-carboxamide, bistrifluoroacetic acid salt*: The product from **Example 62** Part F (30 mg, 0.059 mmol) was treated with TFA according to the procedure described for **Example 1** Part B. The product was isolated by prep HLPC to yield 6.00 mg (24%) of as the title compound. ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.07 (m, 2 H) 1.16 (dd, J = 12.37, 3.57 Hz, 1 H) 1.27 (d, J = 15.40 Hz, 1 H) 1.39 (m, 2 H) 1.57 (m, 2 H) 1.80 (d, J = 12.10 Hz, 1 H) 1.86 (d, J = 11.00 Hz, 3 H) 1.94 (d, J = 11.00 Hz, 1 H) 2.26 (m, 2 H) 2.77 (d, J = 7.15 Hz, 2 H) 2.83 (d, J = 7.15 Hz, 1 H) 3.37 (m, 1 H) 3.78 (s, 1 H) 3.85 (s, 3 H) 5.30 (t, J = 8.25 Hz, 1 H) 6.63 (m, 1 H) 6.81 (m, 1 H) 6.81 (m, 1 H) 7.19 (m, 4 H) 7.24 (t, J = 7.42 Hz, 1 H) 7.28 (m, 3 H) 7.39 (m, 1 H) 7.76 (s, 1 H): MS 433.22 $(M+H)^+$.

[00618] **Examples 63-65** and **89** listed in Table 2 were similarly synthesized by appropriate application of the procedures described for **Example 62** or by straightforward extension of those procedures by one skilled in the art.

Example 66

***trans*-3-(2-((S)-1-(4-(Aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)-benzoic acid, bistrifluoroacetic acid salt**

[00619] The product from **Example 7** (85 mg, 0.18 mmol) was hydrolyzed according to the procedure described for **Example 26**. The crude product was re-dissolved in MeOH/H_2O (9:1) containing 0.1% TFA and evaporated to dryness to yield 86 mg (71%) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (m, 2 H), 1.18 (m, 2 H), 1.48 (m, 1 H), 1.64 (d, J = 12.60 Hz, 1 H), 1.77 (d, J = 11.00 Hz, 3 H), 2.15 (t, J = 12.10 Hz, 1 H), 2.61 (m, 2 H), 3.23 (m, 1 H), 3.42 (m, J = 5.50 Hz, 1 H), 5.37 (bs, 1 H), 7.21 (t, J = 6.32 Hz, 1 H), 7.27 (m, 3 H), 7.63 (t, J = 7.42 Hz, 1 H), 8.00 (m, 3 H), 8.15 (d, J = 6.60 Hz, 1 H), 8.39 (s, 1 H); HRMS $(M+H)^+$ for $C_{26}H_{30}N_4O_3$, calcd m/z: 447.2396, obs: 447.2407.

Examples 67 and 68

Methyl 4-(2-((S)-1-(*trans*-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzoate, bis-trifluoroacetic acid salt (67) and 4-

(2-((S)-1-(*trans*-4-(aminomethyl)cyclohexane-carboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzoic acid, bis-trifluoroacetic acid salt (68)

[00620] *Part A: (S)-ethyl 4-(2-(1-(tert-butoxycarbonyl)-2-phenylethyl)-1H-imidazol-4-yl)benzoate*: The product (8.5 g, 97% over two steps) was synthesized from L-N-(Boc)-phenylalanine (3.99 g, 20 mmol), Cs_2CO_3 (3.25 g, 10 mg), ethyl 4-(2-bromoacetyl)benzoate (5.4 g, 20 mmol) and ammonium acetate (31 g, 400 mmol) by appropriate application of the conditions described for **Example 1** Part A. MS 436.1 $(M + 1)^+$.

[00621] *Part B: Ethyl 4-(2-((S)-1-(trans-4-(aminomethyl)cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)benzoate, bistrifluoroacetic acid salt*: The product from Part A (220 mg, 0.48 mmol) was treated sequentially according to the procedures for **Example 1** Part B, and **Example 2** Part A and Part B to provide 200 mg of product (56% over three steps). MS 334.2 (M-H)-.

[00622] *Part C: Example 67 and 68*: The product from Part B (200 mg, 0.28 mmol) was dissolved in MeOH/H_2O (9:1) containing 0.1% TFA (2 mL). The pH of the solution was adjusted to 12-14 using 1 N aqueous NaOH. The reaction was stirred at rt for 16 h. TFA was added to the solution until it reached pH = 1 and the products were isolated by prep HPLC to yield 66 mg of **Example 67** (34%) and 34 mg of **Example 68** (18%).

[00623] Data for **Example 67**: ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.06 (m, 2 H), 1.38 (m, 2 H), 1.57 (m, 1 H), 1.80 (d, J = 11.55 Hz, 1 H), 1.86 (d, J = 11.55 Hz, 3 H), 2.28 (tt, J = 12.10, 3.30 Hz, 1 H), 2.77 (d, J = 6.60 Hz, 2 H), 3.33 (d, J = 8.25 Hz, 1 H), 3.38 (dd, J = 13.20, 8.00 Hz, 1 H), 3.93 (s, 3 H), 5.33 (t, J = 8.25 Hz, 1 H), 7.18 (d, J = 7.15 Hz, 2 H), 7.23 (t, J = 7.15 Hz, 1 H), 7.29 (t, J = 7.15 Hz, 2 H), 7.77 (d, J = 8.80 Hz, 2 H), 7.89 (s, 1 H), 8.11 (d, J=8.80 Hz, 2 H); HRMS $(M + H)^+$ for $C_{27}H_{32}N_4O_3$, calcd m/z: 461.2523, obs: 461.2570.

[00624] Data for **Example 68**: ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.06 (m, 2 H), 1.39 (m, 2 H), 1.57 (m, 1 H), 1.80 (d, J = 12.10 Hz, 1 H), 1.86 (d, J = 11.55 Hz, 3 H), 2.28 (tt, J = 12.10, 3.30 Hz, 1 H), 2.77 (d, J = 7.15 Hz, 2 H), 3.33 (d, J = 8.25 Hz, 1 H), 3.39 (dd, J = 13.50, 8.25 Hz, 1 H), 5.33 (t, J = 8.25 Hz, 1 H), 7.19 (d, J = 7.15 Hz, 2 H), 7.24 (t, J = 7.15 Hz, 1 H), 7.29 (t, J = 7.15 Hz, 2 H), 7.76 (d, J = 8.25 Hz, 2

H), 7.89 (s, 1 H), 8.12 (d, J = 8.80 Hz, 2 H); HRMS $(M + H)^+$ for $C_{26}H_{30}N_4O_3$, calcd m/z: 447.2396, obs: 447.2397.

Example 69

***trans*-N-((S)-1-(4-(3-Amino-1H-indazol-6-yl)-1H-imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)-cyclohexanecarboxamide, bistrifluoroacetic acid salt**

[00625] The product from **Example 65** (10 mg, 0.022 mmol) was dissolved in 1-butanol. Hydrazine (66 mg, 1.32 mmol) was added and the reaction mixture was heated to 118 °C using microwave irradiation in a sealed tube for 4.5 h. The reaction was cooled to rt and stirred for an additional 8 h. The solvent and excess hydrazine were removed in *vacuo*. The product was re-dissolved in MeOH/H_2O (9:1) containing 0.1% TFA. The solvent was removed under vacuum to provide the title compound (8.8 mg, 59%). HRMS $(M + H)^+$ for $C_{26}H_{31}N_7O$, calcd m/z: 458.2668, obs: 458.2650.

Example 70

***trans*-4-(Aminomethyl)-N-benzyl-N-((S)-2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid salt**

[00626] *Part A: (S)-N-Benzyl-2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine*: The product from **Example 1** Part B (33 mg, 0.1 mmol) and benzaldehyde (16 mg, 0.15 mmol) were dissolved in CH_2Cl_2 (4 mL). $NaBH(OAc)_3$ (32 mg, 0.15 mmol) was added, followed by a few drops of HOAc. The reaction was stirred at rt for 48 h. The reaction was diluted with CH_2Cl_2 and washed with water and brine. It was dried over Na_2SO_4, filtered and evaporated in *vacuo* to give 42 mg, of the crude product. MS 354.5 (M+H)+.

[00627] *Part B: trans-4-(Aminomethyl)-N-benzyl-N-((S)-2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)cyclohexanecarboxamide, bistrifluoroacetic acid sal*: The product from **Example 70** Part A was converted to the title compound following the same procedures described in Example 2 Part A-B. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 0.95 (m, 2 H), 1.25 (m, 1H), 1.60 (m, 3 H), 1.80 (m, 3 H), 2.49 (t, J = 8.52 Hz, 1H),

2.72 (d, J = 7.15 Hz, 2H), 3.53 (d, J = 3.30 Hz, 2 H), 4.80 (m, 2 H), 6.14 (t, J = 8.25Hz, 1 H), 7.00-7.53 (m, 16 H). MS 493.20 $(M + H)^+$.

[00628] **Examples 71-74 and Example 85** listed in Table 5 were synthesized by appropriate application of the procedures described for **Example 70** or by straightforward extension of the procedures described for **Example 70** by one skilled in the art.

Example 77

***trans*-4-Aminomethyl-cyclohexanecarboxylic acid [2-phenyl-1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-amide, bistrifluoroacetic acid salt**

[00629] *Part A: {4-[2-Phenyl-1-(4-phenyl-1H-imidazol-2-yl)-ethylcarbamoyl]-cyclohexyl-methyl-carbamic acid phenyl ester*

The product from **Example 55** Part A (36 mg, 0.1 mmol) was dissolved in THF/DMF (2:1, 6 mL) and cooled to 0 °C. Dicyclohexyl-carbodiimide (162 mg, 0.1 mmol) was added to the solution. The resulting mixture was stirred at 0 °C for 1 h. The product from **Example 1** Part B (33 mg, 0.1 mmol) was added, and the reaction was warmed to 50 °C for 5 h. The reaction was cooled to rt, diluted with EtOAc, washed with water and brine (3X), dried over Na_2SO_4, filtered, and dried in *vacuo*. The title compound was isolated by preparative HPLC to yield 27 mg (40%) as a colorless solid. MS 552.1 $(M+H)^+$.

[00630] *Part B: 4-Aminomethyl-cyclohexanecarboxylic acid [2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amide*: The product from **Example 77** Part A (27 mg mg, 0.04 mmol) was converted to the final product (16 mg, 75%) using the procedure described for **Example 50** Part C. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.09 (m, 2 H), 1.19 (m, 2H), 1.57 (m, 1H), 1.81 (m, 2H) 1.92 (m, 2H), 2.76 (d, J = 6.60 Hz, 2H), 3.25 (m, 1H), 3.35 (m, 2H), 5.21 (t, J = 7.42 Hz, 1H), 7.16 (d, J = 7.15 Hz, 2H), 7.24-7.29 (m, 3H), 7.44-7.49 (m, 3H), 7.65 (d, J = 8.24 Hz, 2H), 7.7 2(s, 1H). MS 418.1 $(M+1)^+$.

Example 82

(S)-4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]amino]-2-phenylethyl]-4-(bromo-1H-imidazol-5-yl)-benzamide

[00631] *Part A: (4-{1-[5-Bromo-4-(4-carbamoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethylcarbamoyl}-cyclohexylmethyl)-carbamic acid tert-butyl ester*: The product from **Example 28** Part A (70 mg, 0.13 mmol) was dissolved in $CHCl_3$ (10 mL) and treated with bromine (21 mg, 0.13 mmol). After stirring for 16 h, the reaction was evaporated to dryness in *vacuo* to yield 93 mg (>99%) of product. MS 625.3/627.3 (1:1; $M+H)^+$.

[00632] *Part B: 4-(2-{1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-bromo-1H-imidazol-4-yl)-benzamide*: The crude product from **Example 82** Part A (93 mg, 0.13 mmol) was converted to the title compound (35.8 mg, 36%) using the procedure described for **Example 2** Part B. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 1.38 (m, 1 H) 1.57 (m, 1 H) 1.76 (d, J = 12.65 Hz, 1 H) 1.85 (d, J = 9.90 Hz, 3 H) 2.23 (dt, J = 12.10, 3.30 Hz, 1 H) 2.77 (d, J = 7.15 Hz, 2 H) 3.20 (dd, J = 13.20, 8.25 Hz, 1 H) 3.26 (dd, J = 13.30, 7.70 Hz, 1 H) 5.23 (t, J = 7.97 Hz, 1 H) 7.17 (d, J = 7.15 Hz, 2 H) 7.21 (d, J = 7.15 Hz, 1 H) 7.26 (t, J = 7.15 Hz, 2 H) 7.75 (d, J = 8.80 Hz, 2 H) 7.95 (d, J = 8.80 Hz, 2 H). MS 524.3/526.3 (1:1; $M + H)^+$.

Example 107

(S)-4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-4-(trifluoromethyl)-1H-imidazol-5-yl]-benzamide, bis-trifluoroacetic acid salt

[00633] *Part A: trans-{4-[(S)-1-(4-Bromo-5-trifluoromethyl-1H-imidazol-2-yl)-2-phenyl-ethylcarbamoyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester*: The product from Part A of **Example 32** was converted to the title compound by sequential application of the procedures described for **Example 1** Part B, **Example 2** Part A and **Example 82** Part A. MS: 573.3/575.3 $(M+1)^+$.

[00634] *Part B: trans-(4-{(S)-1-[4-(4-Carbamoyl-phenyl)-5-trifluoromethyl-1H-imidazol-2-yl]-2-phenyl-ethylcarbamoyl}-cyclohexylmethyl)-carbamic acid tert-butyl ester*: The product from **Example 107** Part A (47 mg, 0.069 mmol), 4-carbamoylphenyl-boronic acid (30 mg, 0.18 mmol), K_3PO_4 (75 mg, 0.35 mmol), and

$Pd(PPh_3)_4$ (22 mg) were added together with 6 mL of 1,4-dioxane. The mixture was heated in a sealed tube in the microwave at 110° C for 1.5.h. The solvent was removed. The residue was dissolved in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica, EtOAc/hexane) to give 25 mg of the desired product. MS: 614.4 $(M+1)^+$.

[00635] *Part C: trans-4-(2-{(S)-1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-trifluoromethyl-1H-imidazol-4-yl)-benzamide, bis-trifluoroacetic acid salt*: The product from **Example 107** Part B was converted to **Example 107** (15 mg) by the appropriate application of the procedure described for **Example 2** Part B. MS: 514.3 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.04 (m, 2H), 1.39 (m, 2H), 1.57 (m, 1H), 1.82 (m, 4H), 2.21 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.20 (m, 2H), 5.25 (m, 1H), 7.20 (m, 5H), 7.50 (d, J = 8.35 Hz, 2H), 7.93 (d, J = 8.79 Hz, 2H).

Example 108

N-{(S)-1-[4-(4-Carbamimidoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-benzamide

[00636] Hydroxylamine hydrochloride (10 eq) was dissolved in DMSO (1 mL) and triethylamine (10 eq) added. The mixture was stirred for 5 min then filtered to remove triethylamine hydrochloride. The compound of **Example 178** Part A (80 mg) was added to the filtrate and the mixture was heated at 65 °C for 1-1.5 h. Reaction was cooled to room temperature, diluted with ~10 mL water, and resulting precipitate collected, washed with water and dried to give the amidoxime intermediate (73 mg, 84%). m/z 426.4 $(M+H)^+$. This material was suspended in methylene chloride (10 mL) and acetic anhydride (0.040 mL) was added. The mixture was stirred for 20 min at room temperature under Argon then evaporated to dryness. The residue was dissolved in a mixture of methanol/HOAc (10:1), 10% Pd/C was added and the mixture was stirred under 1 atm H_2 for 2 h. Catalyst was removed by filtration, filtrate evaporated and residue purified by prep C18 HPLC to provide the bis TFA salt of the title compound (65 mg, 60%) 1H NMR (400 MHz, MeOH-D4) δ 3.41 - 3.59 (m, 2 H) 5.53 (t, J=8.13 Hz, 1 H) 7.20 - 7.31 (m, 5 H) 7.46 (t, J=7.69 Hz, 2 H) 7.56 (t, J=7.47 Hz, 1 H) 7.84 (d, J=7.03 Hz, 2 H) 7.87 - 7.95 (m, 5 H) m/z 410.2 $(M+H)^+$.

Example 109

***trans*-5-(2-{(S)-1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-1H-imidazol-4-yl)-2-cyano-benzoic acid, bistrifluoroacetic acid salt**

[00637] *Part A: 5-Acetyl-2-cyano-benzoic acid methyl ester*: Triflic anhydride (10 g, 35.4 mmol)was added dropwise to a cold (-40 °C) solution of 5-acetyl-2-hydroxy-benzoic acid methyl ester (6.9 g, 35.4 mmol) and DIPEA (5.3 g, 42.5 mmol) in CH_2Cl_2 (100 mL). The reaction was warmed to -10 °C and stirred for 16 h. The reaction was warmed to rt, evaporated to dryness in *vacuo*, and re-dissolved in EtOAc. The organic layer was washed with ½ sat. brine, dried over $MgSO_4$, filtered and evaporated in *vacuo*. A portion of the crude triflate (5.01 g, 15.3 mmol) was dissolved in DMF (40 mL). Palladium (0) tetrakis(triphenylphosphine) (1.3 g, 1.1 mmol) and zinc cyanide (2.16 g, 18.4 mmol) were added to the flask, and the mixture was heated to 90 °C for 2.5 h. The reaction was cooled to rt and stirred with a 1:1 solution of conc. NH_4OH and water (160 mL). The resulting suspension was extracted with ETOAc. The combined organic extracts were washed with ½ sat. brine, dried over $MgSO_4$, filtered and evaporated in *vacuo*. The title compound was isolated by SiO_2 chromatography to yield 439 mg (14%) of a white solid. MS 221.1 $(M+NH_4)^+$.

[00638] *Part B: 5-(2-Bromo-acetyl)-2-cyano-benzoic acid methyl ester*: The product from **Example 109** Part A (107 mg, 0.53 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with bromine (84 mg, 0.53 mmol). The solution changed color from rust red to yellow after 3 h indicating the reaction was complete. The reaction was diluted with CH_2Cl_2, washed with sat'd $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated in *vacuo* to yield 160 mg (>99%) of a colorless solid. ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (s, 3 H) 4.47 (s, 2 H) 7.97 (d, J = 7.70 Hz, 1 H) 8.26 (m, 1 H) 8.69 (s, 1 H).

[00639] *Part C: (S)-2-{[4-(tert-Butoxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}-3-phenyl-propionic acid*: 4-(*tert*-Butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (1.7 g, 6.6 mmol) and ethyl phenylalanine hydrochloride (2.0 g, 6.6 mmol) were dissolved in DMF (30 mL)

and combined with HOAt (0.5 M in DMF, 16 mL, 8 mmol) and 4-methylmorpholine (2.33 g, 23 mmol). To this mixture was added EDCI (1.76 g, 9.2 mmol). The reaction was stirred at rt for 12 h, diluted with EtOAc, washed several times with ½ sat'd brine, dried over MgSO4, filtered and evaporated in *vacuo* to yield 2.8 g (99%) of a colorless solid which was dissolved in MeOH (30 mL) and treated with 1 N NaOH (19 mL) at rt for 3 h. The MeOH was removed in *vacuo* and the residue redissolved in water. The aqueous solution was acidified with 1 N HCl to pH 1 and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo* to yield 2.5 g (95%) of the title compound as the free acid. MS 403.0 (M+H+).

[00640] *Part D: 5-[2-((S)-1-{[4-(tert-Butoxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}-2-phenyl-ethyl)-1H-imidazol-4-yl]-2-cyano-benzoic acid ethyl ester*: The product from **Example 109** Part B (149 mg, 0.53 mmol) and the product from **Example 109** Part D (214 mg, 0.53 mmol) were combined according to the procedure described for **Example 1** Part A to yield 73.6 mg (24%) of the title compound. MS 584.4 $(M-H^+)^-$.

[00641] *Part E: 5-(2-{(S)-1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-1H-imidazol-4-yl)-2-cyano-benzoic acid*: The product from **Example 109** Part B (149 mg, 0.53 mmol) and the product from **Example 109** Part D (214 mg, 0.53 mmol) were combined according to the procedure described for **Example 1** Part A to yield 73.6 mg (24%) of the title compound. MS 584.4 $(M-H^+)^-$.

[00642] *Part F: 5-(2-{(S)-1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-1H-imidazol-4-yl)-2-cyano-benzoic acid*: The product from **Example 109** Part B (13 mg, 0.022 mmol) was dissolved in anhyd. MeOH and cooled to 0 °C. Anhyd. ammonia gas was bubbled into the solution for ca. 15 min, then the reaction vessel was tightly capped and the reaction stirred for 24 h at rt. The reaction was sparged with nitrogen and evaporated to dryness. The crude product was dissolved in 10% TFA in CH_2Cl_2 (v/v) and stirred for 16 h at rt. The solvent and TFA were evaporated in *vacuo*. The crude product was re-dissolved in $MeOH/H_2O$ (9:1) containing 0.1% TFA. The title compound was isolated as a colorless glass via preparative HPLC to yield 2.0 mg (19%). ^1H NMR (500 MHz, d_4-MeOH) □ 1.06 (m, 2 H) 1.39 (m, 2 H) 1.57 (m, 1 H) 1.79 (d, J = 12.10 Hz, 1 H) 1.86 (d, J = 12.10 Hz, 3

H) 2.26 (m, 1 H) 2.77 (d, J = 6.60 Hz, 2 H) 3.33 (d, J = 8.25 Hz, 2 H) 5.32 (t, J = 7.97 Hz, 1 H) 7.19 (d, J = 6.60 Hz, 2 H) 7.22 (m, 1 H) 7.28 (t, J = 7.15 Hz, 3 H) 7.92 (s, 2 H) 8.09 (d, J = 7.70 Hz, 1 H) 8.13 (s, 1 H). MS 472.3 $(M+H^+)^+$.

Example 113

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-bromo-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide, bis-trifluoroacetic acid salt

[00643] Example 113 was synthesized by appropriate application of the procedures described in Example 120, except that the procedure for Example 82 Part A was used in place of the procedure for Example 120 Part D . ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.05 (m, 2 H) 1.39 (m, 2 H) 1.57 (m, 1 H) 1.75 (bd, J=12.10 Hz, 1 H) 1.85 (bd, J=13.20 Hz, 3 H) 2.22 (m, 1 H) 2.77 (d, J=7.15 Hz, 2 H) 3.16 (dd, J=13.20, 8.25 Hz, 1 H) 3.24 (dd, J=13.20, 7.40 Hz, 1 H) 5.21 (t, J=7.97 Hz, 1 H) 7.18 (m, 3 H) 7.25 (t, J=7.42 Hz, 2 H) 7.47 (d, J=9.90 Hz, 1 H) 7.70 (s, 1 H) 7.92 (d, J=8.25 Hz, 1 H). MS: 536 (M+H+)+.

Example 114

(S)-5-[4-(carbamoylphenyl]-2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-1H-imidazole-4-carboxylic acid, methyl ester, bis-trifluoroacetic acid salt

[00644] *Part A: 2-((S)-1-tert-Butoxycarbonylamino-2-phenyl-ethyl)-3H-imidazole-4-carboxylic acid methyl ester*: The compound from Part B of Example 32 (0.42 g, 1.07 mmol) was dissolved in MeOH (8 mL) and TFA (0.8 mL) was added. The mixture was stirred at RT under N_2 for 30 minutes. Aqueous $NaHCO_3$ was added and the MeOH was removed. The aqueous was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried over $MgSO_4$, and concentrated to a yellow foam (0.40 g). LC/MS: 346.4 $(M+1)^+$.

[00645] *Part B: 5-Bromo-2-((S)-1-tert-butoxycarbonylamino-2-phenyl-ethyl)-3H-imidazole-4-carboxylic acid methyl ester*: The product from Example 114 Part A (1.2 g of 83% pure, 0.28 mmol) was dissolved in $CHCl_3$ (20 mL) and NBS (0.93 g,

0.41 mmol) was added. The mixture was stirred at RT under N_2 for 1.5 h. It was diluted with $CHCl_3$ and washed with water and brine. It was then dried over $MgSO_4$ and concentrated to a white solid (0.79 g). MS: 424.4/426.2 $(M+1)^+$.

[00646] *Part C: trans-5-Bromo-2-((S)-1-{[4-(tert-butoxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}-2-phenyl-ethyl)-3H-imidazole-4-carboxylic acid methyl ester*: The product from Example 114 Part B was converted to the title compound by sequential application of the procedures described for Example 1 Part B and Example 2 Part A. LC/MS: 563.3 $(M+1)^+$.

[00647] *Part D: trans-2-{(S)-1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-(4-carbamoyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester, bis-trifluoroacetic acid salt*: The product from Example 114 Part C was converted to Example 114 by sequential application of the procedures described for Example 107 Part B and Example 2 Part B. MS: 504.4 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.39 (m, 2H), 1.57 (m, 1H), 1.81 (m, 4H), 2.23 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.24 (m, 2H), 3.82 (s, 3H), 5.28 (t, J = 7.91 Hz, 1H), 7.21 (m, 5H), 7.76 (d, J = 8.35 Hz, 2H), 7.94 (d, J = 8.35 Hz, 2H).

Example 117

(S)-N-[1-[4-[4-(carbamoyl)phenyl]-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)- benzamide

[00648] This compound was prepared by appropriate application of the methods described in Example 28. MS: 440.2 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 3.53 (m, 2H), 4.19 (s, 2H), 5.55 (m, 1H), 7.27 (m, 5H), 7.57 (m, 2H), 7.77 (m, 2H), 7.80-8.02 (m, 5H).

Example 118

4-Aminomethyl-*N*-{(S)-1-[4-(4-carbamoyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-2-fluoro-benzamide

[00649] Example 118 was prepared by appropriate application of the methods described in Example 28. MS: 458.2 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 3.47 (dd, J = 13.84 and 8.13 Hz, 2H), 4.18 (s, 2H), 5.59 (t, J = 7.91 Hz, 1H), 7.29 (m, 7H), 7.77 (m, 3H), 7.89 (s, 1H), 7.98 (d, J = 8.79 Hz, 2H).

Example 119

***trans*-2-{(S)-1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-(4-carboxy-phenyl)-3*H*-imidazole-4-carboxylic acid, bis-trifluoroacetic acid salt**

[00650] The product from Example 114 was hydrolyzed with LiOH/THF to give the Example 119. MS: 491.4 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.05 (dd, J = 12.52 and 4.17 Hz, 2H), 1.39 (m, 2H), 1.57 (m, 1H), 1.85 (m, 4H), 2.23 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.23 (m, 2H), 5.29 (t, J = 7.91 Hz, 1H), 7.21 (m, 5H), 7.81 (d, J = 8.35 Hz, 2H), 8.06 (d, J = 8.79 Hz, 2H).

Example 120

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide, bis-trifluoroacetic acid salt

[00651] *Part A: 4-Cyano-3-fluorobenzoic acid*: 4-Bromo-3-fluorobenzoic acid (7.5 g, 0.034 mol), $Zn(CN)_2$ (4.0 g, 0.034 mol) and $Pd(PPh_3)_4$ (3.95 g, 0.0034 mol) were added together with 60 mL of DMF (degassed). The mixture was heated at 90 °C under N_2 for 3 h. It was cooled to room temperature and filtered to remove insoluble inorganic salts (discarded). The filtrate was diluted with water and extracted with EtOAc. The EtOAc mixture was washed with water, brine, dried over $MgSO_4$, and concentrated to yield 4.5 g of the desired product with 90% purity. This material was taken into the next step without further purification. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 7.82 (m, 1H), 7.90 (m, 3H), 7.56 (d, J = 10.0 Hz, 1H), 7.68 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H).

[00652] *Part B: 4-(2-Bromoacetyl)-2-fluorobenzonitrile*: 4-Cyano-3-fluorobenzoic acid (4.0 g of 90% pure material, 0.02 mol) was dissolved in CH_2Cl_2 (50 mL). To it was added dropwise oxalyl chloride over 15 minutes (2.3 mL, 0.026 mol). The mixture was stirred at rt for 1 h and then heated at reflux for 1 h under N_2. The solvent was removed, and the residue was redissolved in CH_3CN (50 mL). This solution was cooled to -15 °C, and to it was added (trimethylsilyl)diazomethane (11.5 mL of 2.0M in hexane) dropwise over 20 minutes. The resulting mixture was stirred

at -15 °C for 1 h under N_2. To it was added dropwise a solution of HBr in HOAc (4.25 mL of 33% wt) over 20 minutes, and the reaction mixture was stirred at -15 °C for 20 minutes. The solvent was removed, and the residue was dissolved in EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated to 3.2 g of the desired product. MS: 240.1, 242.1, $(M+H)^+$. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 2.42 (s, 2H), 7.76-7.85 (m, 3H).

[00653] *Part C: tert-butyl (S)-1-(4-(4-cyano-3-fluorophenyl)-1H-imidazol-2-yl)-2-phenylethylcarbamate*: 4-(2-Bromoacetyl)-2-fluorobenzonitrile (3.2 g 0.013 mol), L-Boc-phenylalanine (3.5 g, 0.013 mol), and Cs_2CO_3 (2.6 g, 0.008 mol) were added together with DMF (20 mL). The mixture was stirred at 15 °C for 1 h under N_2. It was diluted with 100 mL of EtOAc, washed with water, brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (120 g x 2 silica, 10-55% EtOAc in hexane) to give 3.5 g of the desired ester. LC/MS: 425.3. This material was then combined with ammonium acetate (12 g) and suspended in xylenes (100 mL). The mixture was heated under N_2 at 150 °C for 2.5 h in a flask equipped with a Dean-Stark trap. The xylenes were removed. The residue was dissolved in EtOAc, and washed with water and brine. It was dried over $MgSO_4$, concentrated, and purified by flash chromatography (120 g x 2 silica, 15-70% EtOAc in hexane) to give 2.2 g of the desired imidazole. MS: 407 $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.30 (m, 2H), 4.86 (d, J = 6.59 Hz, 1H), 5.32 (d, J = 7.47 Hz, 1H), 7.14-7.24 (m, 6H), 7.53-7.61 (m, 3H).

[00654] *Part D: tert-butyl (S)-1-(5-chloro-4-(4-cyano-3-fluorophenyl)-1H-imidazol-2-yl)-2-phenylethylcarbamate*: The product from Example 120 Part C (2.2 g, 5.4 mmol) and N-chlorosuccinimide (0.80 g, 6.7 mmol) were added together with CH_3CN (100 mL). The mixture was heated at reflux for 7 h under N_2. The solvent was removed, and the residue was dissolved in EtOAc. It was washed with water, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give 2.4 g of foam. MS: 441.3, $(M+H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 3.23 (m, 2H), 4.89 (m, 1H), 5.46 (d, J = 7.03 Hz, 1H), 7.07 (d, J = 6.15 Hz, 2H), 7.25-7.26 (m, 5H), 7.54 (m, 1H).

[00655] *Part E: 4-(2-((S)-1-amino-2-phenylethyl)-5-chloro-1H-imidazol-4-yl)-2-fluorobenzonitrile*: The product from Example 120 Part D (0.20 g, 0.45 mmol) was

stirred with CH_2Cl_2 (6 mL) and TFA (1.5 mL) under N_2 for 0.5 h. The solvents were removed. The residue was dried under vacuum to give 0.26 g of the bis-TFA salt. MS: 340.94, $(M+H)^+$. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 3.33 (m, 2H), 4.56 (dd, J = 8.57, 6.37 Hz, 1H), 7.12 (d, J = 6.59 Hz, 2H), 7.25-7.30 (m, 3H), 7.67 (m, 2H), 7.81 (m, 1H).

[00656] *Part F: trans-(4-{(S)-1-[5-Chloro-4-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethylcarbamoyl}-cyclohexylmethyl)-carbamic acid tert-butyl ester*: Boc-tranexamic acid (0.14 g, 0.54 mmol), Bop reagent (0.24 g, 0.54 mmol) and TEA (0.38 mL, 2.7 mmol) were added together with 10 mL of THF. The mixture was stirred at rt for 15 minutes under N_2, and the product from **Example 120** Part E (0.26 g, 0.45 mmol) was added. The resulting mixture was heated at 75 °C for 15 minutes under N_2. The reaction mixture was cooled to rt and the solvent was removed. The residue was dissolved in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, and purified by flash chromatography (40 g silica, 10-100% EtOAc in hexane) to give 0.21 g of the desired product. MS: 580.3, $(M+H)^+$. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 0.94 (m, 2H), 1.25-1.37 (m, 4H), 1.42 (s, 9H), 1.76-1.79 (m, 3H), 2.15 (m, 1H), 2.85 (m, 2H), 3.20-3.30 (m, 2H), 5.17 (m, 1H), 7.16-7.23 (m, 5H), 7.67-7.80 (m, 3H).

[00657] *Part G: trans-4-Aminomethyl-cyclohexanecarboxylic acid {(S)-1-[5-chloro-4-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-amide*: The product from **Example 120** Part F (0.21 g, 0.36 mmol) was stirred with CH_2Cl_2 (8 mL) and TFA (2 mL) under N_2 for 0.5 h. The solvents were removed. The residue was dried under vacuum to give 0.25 g of the bis-TFA salt. MS: 480.3, $(M+H)^+$.

[00658] *Part H: trans-4-Aminomethyl-cyclohexanecarboxylic acid {(S)-1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenyl-ethyl}-amide, bis-trifluoroacetic acid salt*: The product from **Example 120** Part G (0.21 g, 0.36 mmol) and hydrazine monohydrate (0.69 mL) were added together with 8 mL of n-butanol. The mixture was heated at 120 °C under N_2 for 1 h. The solvent was removed. The residue was purified by reverse phase HPLC to give 0.14 g of the title compound as the bis-TFA salt. MS: 492.3, $(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.82-0.84 (m, 2H), 1.11-1.22 (m, 2H), 1.36 (m, 1H), 1.52 (m, 1H), 1.61-1.70 (m, 3H), 2.02 (m,

1H), 2.52-2.61 (m, 2H), 2.94-3.09 (m, 2H), 5.15 (m, 1H), 7.13-7.20 (m, 5H), 7.77-8.27 (m, 3H).

Example 121

N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)benzamide, bis-trifluoroacetic acid salt

[00659] **Example 121** was prepared by the appropriate application of the procedures described for **Example 120**, where 4-((tert-butoxycarbamoyl)methyl)benzoic acid instead of Boc-tranexamic acid was used in **Example 120** Part F. MS: 486.3, $(M+H)^+$. ^{1}HNMR (500 MHz, d_4-MeOH) δ 3.33-3.35 (m, 2H), 4.18 (s, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.22-7.25 (m, 5H), 7.52-7.55 (m, 3H), 7.72 (s, 1H) 7.88 (d, J = 8.25 Hz, 2H), 7.97 (d, J = 8.80 Hz, 1H).

Example 122

3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-1H-indazole-6-carboxamide, bis-trifluoroacetic acid salt

[00660] *Part A: tert-Butyl (S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethylcarbamate*: The product from part D of **Example 120** (0.52 g, 1.2 mmol) was converted to the aminoindazole by appropriate application of the method described in Part H of **Example 120**. MS: 453.3 $(M+H)^+$.

Part B: 6-(2-((S)-1-amino-2-phenylethyl)-5-chloro-1H-imidazol-4-yl)-1H-indazol-3-amine: The Boc protecting group in the product from **Example 122** Part A was removed with TFA as described in Part G of **Example 120**. LC/MS: 353.1 $(M-H)^+$.

[00661] *Part C: N-((S)-1-(4-(3-Amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-4-cyano-3-fluorobenzamide*: The product from **Example 122** Part B was coupled with 4-cyano-3-fluorobenzoic acid using the methods described in Part F of **Example 120**. MS: 500.3 $(M+H)^+$.

[00662] *Part D: 3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-1H-indazole-6-carboxamide, bis-trifluoroacetic acid salt*: The product from **Example 122** Part C was converted to **Example 122** using the method described in Part H of **Example 120**. MS: 510.3 $(M-H)^-$. ^{1}HNMR (400 MHz,

d_4-MeOH) δ 3.37 (m, 2H), 5.45 (t, J = 7.42 Hz, 1H), 7.23-7.27 (m, 5H), 7.54-7.58 (m, 2H), 7.72 (s, 1H), 7.86 (s, 1H), 7.91-7.97 (m, 2H).

Example 123

3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)benzo[d]isoxazole-6-carboxamide, bis-trifluoroacetic acid salt

[00663] The product from Part C of **Example 122** was converted to the aminobenzisoxazole with acetohydroxamic acid and potassium carbonate in DMF. MS: 513.1 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 3.37 (m, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.23-7.27 (m, 5H), 7.54 (d, J = 8.79 Hz, 1H), 7.68 (d, J = 8.24Hz, 1H), 7.72 (s, 1H), 7.82 (d, J = 8.24 Hz, 1H), 7.83 (s, 1H), 7.97 (d, J = 8.79 Hz, 1H).

Example 124

N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)-2-fluorobenzamide, bis-trifluoroacetic acid salt

[00664] **Example 124** was prepared by appropriate application of the procedures described for **Example 120**, where 4-cyano-2-fluorobenzoic acid instead of Boc-tranexamic acid was used in **Example 120** Part F. The cyano group was reduced with $(Boc)_2O/NiCl_2/NaBH_4$ in MeOH at 0 °C. The title compound was isolated as the bis-TFA salt after TFA deprotection by appropriate application of the procedure described for **Example 2** Part B. MS: 504.1, $(M+H)^+$. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 3.34 (m, 2H), 4.18 (s, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.20-7.27 (m, 5H), 7.33-7.35 (m, 2H), 7.54 (dd, J = 8.34 Hz and 1.31 Hz, 1H), 7.75 (m, 2H), 7.97 (d, J = 9.22 Hz, 1H).

Example 128

N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-4-chloro-2-fluorobenzamide, bis-trifluoroacetic acid salt

[00665] **Example 128** was prepared similarly by appropriate application of the procedures for **Example 120**, where 4-chloro-2-fluorobenzoic acid instead of Boc-tranexamic acid used in **Example 120** Part F. MS: 509.3, $(M+H)^+$. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 3.34 (m, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.21-7.34 (m, 7H), 7.53

(dd, J = 8.79 Hz and 1.1 Hz, 1H), 7.66 (t, J = 8.24 Hz, 1H), 7.72 (s, 1H), 7.99 (d, J = 8.79 Hz, 1H).

Example 129

N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-2-fluoro-5-methoxybenzamide, bis-trifluoroacetic acid salt

[00666] Example 121 was prepared similarly by appropriate application of the procedures described for Example 120, where 2-fluoro-5-methoxybenzoic acid instead of Boc-tranexamic acid used in Example 120 Part F. MS: 505.3, $(M+H)^+$. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 3.34 (m, 2H), 3.78 (s, 3H), 5.44 (t, J= 7.42 Hz, 1H), 7.06 (m, 1H), 7.12 (m, 1H), 7.19 (m, 1H), 7.23-7.27 (m, 5H), 7.55 (dd, J = 8.79 Hz and 1.1 Hz, 1H), 7.73 (s, 1H), 7.98 (d, J = 8.79 Hz, 1H).

Example 130

(S)-4-[2-[(1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-4-chloro-1H-imidazol-5-yl]-benzamide, bis-trifluoroacetic acid salt

[00667] The product from Part A of Example 28 was chlorinated with NCS/$CHCl_3$ at RT using the procedure described in Example 120 Part D. The Boc group was then removed using the procedure for Example 2 Part B to give the final product as the bis-TFA salt. MS: 506.2 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.38 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.85 (d, J = 10.55 Hz, 3H), 2.20 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.17 (m, 2H), 5.20 (t, J = 7.91 Hz, 1H), 7.21 (m, 5H), 7.73 (d, J = 8.79 Hz, 2H), 7.92 (d, J = 8.79 Hz, 2H).

Example 131

***trans*-Cyclohexane-1,4-dicarboxylic acid 1-amide 4-({(S)-1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-amide), bis-trifluoroacetic acid salt**

[00668] Example 131 was prepared similarly by appropriate application of the procedures for Example 120, where 4-*trans*-(methoxycarbonyl)cyclohexanecarboxylic acid instead of Boc-tranexamic acid was used in Example 120 Part F. The intermediate methyl ester was then converted to the

amide by sequential application of the procedures used for Example 26 Part A and Example 44 Part A. MS: 506.2 , $(M+H)^+$. ^{1}HNMR (500 MHz, d_4-MeOH) δ 1.33-1.38 (m, 1H), 1.45-1.48 (m, 3H), 1.72 (m, 1H) 1.88 (m, 3H), 2.18-2.23 (m, 2H), 3.17 (m, 1H), 3.26 (m, 1H), 5.21 (t, J = 7.42 Hz, 1H), 7.19 (m, 3H), 7.25 (m, 2H), 7.52 (dd, J = 8.24 Hz and 1.1 Hz, 1H), 7.70 (s, 1H), 7.99 (d, J = 8.24 Hz, 1H).

Example 132

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-1,4-benzenedicarboxamide, bis-trifluoroacetic acid salt

[00669] Example 132 was prepared by appropriate application of the procedures described for Example 120 wherein 4-carbamoylbenzoic acid was used instead of Boc-tranexamic acid in Example 120 Part F. MS: 500.1, $(M+H)^+$. ^{1}H-NMR (500 MHz, d_4-MeOH) δ 3.34 (m, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.24-7.26 (m, 5H), 7.54 (dd, J = 8.79 and 1.1 Hz, 1H), 7.72 (s, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 8.79 Hz, 1H).

Example 135

(S)-4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-4-phenyl-1H-imidazol-5-yl]-benzamide, bis-trifluoroacetic acid salt

[00670] The product from Part A of Example 28 was converted to (4-{(S)-1-[5-Bromo-4-(4-carbamoyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethylcarbamoyl}-cyclohexylmethyl)-carbamic acid *tert*-butyl ester by appropriate application of the procedure for Example 82 Part A. This compound was then coupled with phenyl boronic acid by appropriate application of the conditions described for Example 107 Part B. Deprotection of the Boc group with TFA using the procedure from Example 2 Part B afforded the Example 135 as the bis-TFA salt. MS: 522.4 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ δ 1.07 (m, 2H), 1.42 (m, 2H), 1.59 (m, 1H), 1.85 (m, 4H), 2.30 (m, 1H), 2.78 (d, J = 6.59 Hz, 2H), 3.41 (m, 2H), 5.32 (t, J = 8.13 Hz, 1H), 7.29 (m, 7H), 7.44 (m, 2H), 7.90 (d, J = 8.35 Hz, 2H).

Example 136

1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-isoquinoline-6-carboxamide, bis-trifluoroacetic acid salt

[00671] This product was prepared using 1-aminoisoquinoline-6-carboxylic acid from Part D of **Example 147** and the product from Part E of **Example 120** by sequential application of the procedures described for **Example 147** Part F and **Example 120** Part F. MS: 523.2 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 3.39 (dd, J = 15.82, 7.91 Hz, 2H) ,5.48 (t, J = 7.91 Hz, 1H), 7.25-7.27 (m, 6H), 7.52 (d, J = 10.11 Hz, 1H), 7.61 (d, J = 7.03 Hz, 1H), 7.72 (s, 1H), 7.96 (d, J = 8.35 Hz, 1H), 8.08 (dd, J = 8.79, 1.76 Hz, 1H) ,8.30 (s, 1H) ,8.49 (d, J = 8.79 Hz, 1H).

Example 137

1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-5,6,7,8-tetrahydroisoquinoline-6-carboxamide, bis-trifluoroacetic acid salt

[00672] **Example 137** was prepared from the product of Part F of **Example 147** by appropriate application of the procedures for **Example 120** Part H. MS: 527.3 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 2.44 (m, 2H), 2.76(m, 2H), 2.88 (m, 1H), 3.21 (m, 2H), 3.34 (m, 2H) 5.29 (m, 1H), 6.66 (t, J = 7.9 Hz, 1H), 7.24 (m,5H), 7.56 (m, 2H), 7.73 (s, 1H), 7.97 (d, J = 7.9 Hz, 1H).

Example 138

2-(3-amino-1H-indazol-6-yl)-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)acetamide, bis-trifluoroacetic acid salt

[00673] This compound was prepared by appropriate application of the methods described for **Example 122**, wherein 2-(4-cyano-3-fluorophenyl)acetic acid ws replaced by 4-cyano-3-fluorobenzoic acid. MS: 526.3 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 3.17(m, 1H), 3.26 (m, 1H), 3.69(d, J = 5.71 Hz, 2H), 5.26 (t, J = 7.03 Hz, 1H), 7.02 (d, J = 8.34 Hz, 1H), 7.16 (m,5H), 7.26 (s, 1H), 7.52 (d, J = 8.79 Hz, 1H), 7.71(s, 1H), 7.81 (d, J = 8.34 Hz, 1H), 7.97(d, J = 8.79 Hz, 1H).

Example 139

***trans*-4-(2-{(S)-1-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-bromo-1-methyl-1*H*-imidazol-4-yl)-benzamide, bis-trifluoroacetic acid salt**

[00674] The product from **Example 82** Part A was methylated with MeI/K_2CO_3/DMF. The major isomer isolated was deprotected using the procedure described for **Example 2** Part B to give **Example 139**. MS: 538.2/540.2 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.04 (m, 2H), 1.39 (m, 2H), 1.56 (m, 1H), 1.80 (m, 4H), 2.20 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.27 (m, 2H), 3.41 (s, 3H), 5.35 (t, J = 7.91 Hz, 1H), 7.22 (m, 5H), 7.96(m, 4H).

Example 140

4-Aminomethyl-*N*-{(S)-1-[4-(4-carbamoyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-2-ethylamino-benzamide, bis-trifluoroacetic acid salt

[00675] *Part A: tert-Butyl 4-cyano-2-fluorobenzoate*: 4-Cyano-2-fluorobenzoic acid (1.0 g, 6.1 mmol) was dissolved in t-BuOH (9 mL) and THF (3 mL). Boc anhydride (2.64 g, 12.1 mmol) was added followed by DMAP (0.24 g, 1.97 mmol). The mixture was stirred at RT under N_2 for 12 h. The solvents were removed. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. It was dried over $MgSO_4$ and concentrated to an oil which became solid under vacuum (1.3 g). ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.59 (s, 9H), 7.44 (dd, J = 25.71 and 9.01 Hz, 2H), 7.95 (m, 1H).

[00676] *Part B: tert-Butyl 4-cyano-2-(ethylamino)benzoate*: The product from **Example 140** Part A (0.30 g, 1.36 mmol) and ethylamine hydrochloride (0.22 g, 2.72 mmol) were added together with 5 mL of DMF. The mixture was heated at 50 °C under N_2 for 2 h. Water was added, and the mixture was extracted with EtOAc. The EtOAc extract was washed with brine, dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography (silica, EtOAc/hexane) to give 50 mg of the desired product. MS: 247.3 $(M+1)^+$.

[00677] *Part C: 4-Cyano-2-(ethylamino)benzoic acid*: The product from **Example 140** Part B (50 mg, 0.20 mmol) was stirred with 5 mL of TFA and 5 mL of

CH_2Cl_2 at RT for 1 h, and then heated at reflux for 1 h under N_2. The solvent was removed. The residue was dried to give 45 mg of the acid. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.28 (m, 3H), 3.18 (m, 2H), 76.75 (m, 1H), 6.86 (s, 1H), 7.95 (d, J = 7.91 Hz, 1H).

[00678] *Part D: (S)-4-(2-(1-(1-(4-Cyano-2-(ethylamino)phenyl)vinylamino)-2-phenylethyl)-1H-imidazol-4-yl)benzamide*: Cyano-2-(ethylamino)benzoic acid from **Example 140** Part C (40 mg, 0.2 mmol) , Bop reagent (108 mg, 0.24 mmol), and Et_3N (0.28 mL) were added together with 5 mL of THF. The mixture was stirred at RT for 15 minutes and (S)-4-(2-(1-Amino-2-phenylethyl)-1H-imidazol-4-yl)benzamide (107 mg, 0.2 mmol), obtained from N-boc-(L)-phenylalanine and 4-(2-Bromo-acetyl)-benzonitrile by the sequential application of the procedures described for **Example 1** Part A, **Example 28** Part A and **Example 1** Part B, was added. The resulting mixture was heated to reflux under N_2 for 2 h. The solvent were removed. The residue was dissolved in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, and purified by ISCO flash chromatography (silica, EtOAc/hexane) to give 50 mg of the desired product. LC/MS: 479.3 $(M+1)^+$.

[00679] *Part E: 4-Aminomethyl-N-{(S)-1-[4-(4-carbamoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-2-ethylamino-benzamide, bis-trifluoroacetic acid salt*: The product from **Example 140** Part D was dissolved in 10 mL of MeOH and 1 mL of 4N HCl in dioxane. Catalytic amount of Pd/C (10%) was added. The mixture was placed under a balloon of H_2 for 12 h. It was filtered through Celite, concentrated, and purified by reverse phase HPLC to give 24 mg of bis-TFA salt. LC/MS: 483.4 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.22 (t, J = 7.25 Hz, 3H), 3.18 (q, J = 7.03 Hz, 2H), 3.47 (dd, J = 32.52 and 8.35 Hz, 2H), 4.05 (s, 2H), 5.50 (t, J = 8.35 Hz, 1H), 6.66 (d, J = 7.91 Hz, 1H), 6.77 (s, 1H), 7.26 (m, 5H), 7.70 (d, J = 7.91 Hz, 1H), 7.76 (d, J = 8.35 Hz, 2H), 7.88 (s, 1H), 7.98 (d, J = 8.35 Hz, 2H).

Example 142

(S)-N-(1-(4-(4-Carbamoylphenyl)-1H-imidazol-2-yl)-2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide

[00680] **Example 142** was prepared by appropriate application of the methods described in **Example 28**. MS: 466.2 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 3.15

(t, J = 6.37 Hz, 2H), 3.49 (m, 4H), 4.41 (s, 2H), 5.53 (t, J = 8.35 Hz, 1H), 7.27 (m, 6H), 7.75 (m, 4H), 7.88 (s, 1H), 7.97 (d, J = 8.79 Hz, 2H).

Example 143

4-Aminomethyl-*N*-[(S)-1-[4-(4-carbamoyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl]-2-ethyl-benzamide

[00681] *Part A: Methyl 4-bromo-2-chlorobenzoate*: 2-Bromo-4-chlorobenzoic acid (1.0 g, 4.25 mmol) was dissolved in 10 mL of MeOH. The mixture was cooled in an ice-bath and to it was added thionyl chloride (3.1 mL, 42.5 mmol) dropwise. The cooling bath was removed and the mixture was stirred at rt under N_2 for 12 h. The solvent was removed and dried under vacuum to give 1.0 g of colorless oil. LC/MS: 251.1 $(M+1)^+$.

[00682] *Part B: Methyl 2-chloro-4-cyanobenzoate*: The product from **Example 143** Part A (1.0 g, 4.0 mmol), $Zn(CN)_2$ (0.52 g, 4.8 mmol), $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol) were added together with 9 mL of DMF. The mixture was degassed and then heated at 90 °C for 6 h. Water and EtOAc were added to the reaction mixture. It was filtered to remove inorganic solids. The layers were separated and the EtOAc layer was washed with water and brine. It was dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica, EtOAc/hexane) to give 0.28 g of the desired product. MS: 196.1 $(M+1)^+$.

[00683] *Part C: Methyl 4-cyano-2-ethylbenzoate*: The product from **Example 143** Part B (160 mg, 0.82 mmol), ethyl boronic acid (120 mg, 1.64 mmol), K_3PO_4 (344 mg (1.64 mmol), and $Pd(PPh_3)_4$ (114 mg, 0.1 mmol) were added together with 9 mL of DME. The mixture was heated at 150 °C in a microwave for 15 minutes. The DME was removed and EtOAc was added. It was washed with water and brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica, EtOAc/hexane) to give 100 mg of the desired product. MS: 190.21 $(M+H^+)^+$ and 222.3 $(M+Na^+)^+$.

[00684] *Part D: 4-Cyano-2-ethylbenzoic acid*: The product from **Example 143** Part C (100 mg, 0.53 mmol) was dissolved in 5 mL of EtOH and 1 mL of 1N aqueous NaOH was added. The mixture was stirred at RT under N_2 for 2 h. Aqueous 1N HCl

was added to adjust the pH to 4. The EtOH was removed, and the mixture was diluted with EtOAC and water. The two layers were separated. The water layer was extracted with EtOAc. The combined EtOAc solution was washed with water and brine, dried over $MgSO_4$, and concentrated to give 90 mg of the desired acid. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.22 (m, 3H), 3.00 (m, 2H), 7.71 (m, 1H), 7.67 (s, 1H), 7.92 (d, J = 8.35 Hz, 1H).

[00685] *Part E: N-{(S)-1-[4-(4-Carbamoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-4-cyano-2-ethyl-benzamide*: The product from Example 143 Part D (90 mg, 0.51 mmol), Bop reagent (265 mg, 0.61 mmol), and triethylamine (0.42 mL, 1.5 mmol) were added together with 5 mL of THF. The mixture was stirred at RT under N_2 for 15 minutes and (S)-4-(2-(1-amino-2-phenylethyl)-1H-imidazol-4-yl)benzamide prepared using the methods described in Examples 2 and 28 (365 mg, 0.51 mg) was added. The resulting mixture was heated at 75 °C for 70 minutes. The THF was removed, and the residue was dissolved in EtOAc. It was washed with waster and brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica, EtOAc/hexane) to give 80 mg of the desired product. MS: 464.4 $(M+1)^+$.

[00686] *Part F: 4-Aminomethyl-N-{(S)-1-[4-(4-carbamoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-2-ethyl-benzamide*: The product from Example 143 Part B (70 mg, 0.15 mmol) was dissolved in 10 mL of MeOH and 1 mL of 4 N HCl in dioxane. Catalytic amount of Pd/C (10%) was added and the mixture was placed under a balloon of H_2 for 6 h. It was filtered through Celite and washed with MeOH. The filtrate was concentrated and purified by reverse phase HPLC to give 75 mg of the bis-TFA salt. LC/MS: 468.4 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.08 (t, J = 7.47 Hz, 3H), 2.61 (t, J = 7.47 Hz, 2H,), 3.44 (dd, J = 13.62, 8.35 Hz, 2H), 4.12 (s, 2H), 5.59 (t, J = 8.35 Hz, 1H), 7.34 (m, 7H), 7.80 (d, J = 8.35 Hz, 2H), 7.89 (s, 1H), 7.99 (d, J = 8.35 Hz, 2H).

Example 144

3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-1-methyl-1H-indazole-6-carboxamide, bis-trifluoroacetic acid salt

[00687] The product from Part C of Example 122 was converted to the desired product by appropriate application of the method described in Part H of Example

120, where methyl hydrazine was used instead of hydrazine. MS: 526.3 $(M+H)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 3.35 (m, 2H), 3.84 (s, 3H), 5.46 (m, 1H), 7.23 (m, 5H), 7.39 (d, J = 8.35 Hz, 2H), 7.64 (s, 1 H), 7.72 (d, J = 8.35 Hz, 1H), 7.79 (s, 1H), 7.84 (d, J = 7.91 Hz, 1H).

Example 147

1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-5,6,7,8-tetrahydroisoquinoline-6-carboxamide, bis-trifluoroacetic acid salt

[00688] *Part A: (E)-2-(2-(Dimethylamino)vinyl)terephthalonitrile*: Methylterephthalonitrile (1.42 g, 1.0 mmol) and t-butoxybis(dimethylamine)methane (3.5 g, 2.0 mmol) were heated with 15 mL of DML at 75 °C for 12 h under N_2. The DMF was removed and hexane was added. The precipitate formed was filtered and dried to give 1.85 g of the desired product. MS: 504.4, $(M+H)^+$. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 2.95 (s, 6H), 5.27 (d, J = 13.62 Hz, 1H), 7.14 (m, 1H), 7.42 (d, J = 13.18 Hz, 1H), 7.54 (d, J = 7.91 Hz, 1H), 7.86 (s, 1H).

[00689] *Part B: 2-(2,4-Dimethoxybenzyl)-1-imino-1,2-dihydroisoquinoline-6-carbonitrile*: The product from Example 147 Part A (1.85 g, 9.38 mmol) and 2,4-dimethoxybenzylamine (2.6 mL, 15.03 mmol) were heated with 5 mL of DMPU at 140 °C for 3 h under N_2. The reaction mixture was cooled, and EtOAc/hexane(1:2) was added. The precipitate formed was filtered and dried in *vacuo* to give 2.5 g of the desired product. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.72 (s, 3H, 3.81 (s, 3H), 4.95 (s, 2H), 6.10 (d, J = 7.03 Hz, 1H, 6.44 (d, J = 7.91 Hz, 1H), 6.57 (s, 1H), 7.02 (d, J = 8.35 Hz, 1H), 7.22 (d, J = 6.15 Hz, 1H,) 7.68 (d, J = 7.91 Hz, 1H), 7.94 (s, 1H), 8.34 (d, J = 7.91 Hz, 1H).

[00690] *Part C: 2-(2,4-Dimethoxybenzyl)-1-imino-1,2-dihydroisoquinoline-6-carboxylic acid*: The product from Example 147 Part B (2.5 g, 7.84 mmol) was heated with 40 mL of MeOH-15% NaOH (1:1) at 90 °C for 1.5 h under N_2. The reaction mixture was cooled and aq. HCl was added dropwise to adjust the pH to about 5. The methanol was removed and EtOAc/hexane (1:2) were added. The precipitate formed was filtered and dried to give 2.42 g of the desired product.

LC/MS: 339.2, $(M+H)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 2.00 (s, 2H), 3.82 (d, J = 9.67 Hz, 6H), 6.62 (m, 2H), 7.23 (d, J = 7.91 Hz, 2H), 7.50 (d, J = 7.03 Hz, 1H), 8.23 (s, 1H), 8.31 (s, 1H), 8.42 (d, J = 8.79 Hz, 1H).

[00691] *Part D: 1-Aminoisoquinoline-6-carboxylic acid*: The product from Example 147 Part C (2.12g, 6.28 mmol) was heated with 17 mL of anisole and 20 mL of TFA at 105 °C for 12 h under N_2. The solvents were removed, and EtOAc/hexane(1:2) were added. The precipitate formed was filtered and dried to give 1.77 g of the TFA salt. LC/MS: 189.04, $(M+H)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 7.34 (d, J = 7.03 Hz, 1H), 7.62 (d, J = 7.03 Hz, 1H), 8.30 (d, J = 8.79 Hz, 1H), 8.51 (d, J = 8.79 Hz, 1H), 8.56 (s, 1 H).

[00692] *Part E: 1-Amino-5,6,7,8-tetrahydroisoquinoline-6-carboxylic acid*: The product from Example 147 Part D (1.0 g, 3.31 mmol) and platinum oxide (87 mg, 0.38 mmol) were added together with 21 mL of TFA. The reaction mixture was placed under a balloon of hydrogen gas and then warmed to 60 °C for 16 h. The mixture was cooled to RT and filtered through Celite to remove platinum oxide. The solvent was removed, and the residue was purified by reverse phase HPLC to give 0.21 g of the desired product as the TFA salt. LC/MS: 193.1, $(M+H)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 2.00 (m, 1H), 2.28 (m, 1H), 2.57 (m, 2H,) 2.85 (m, 1H), 3.02 (d, J = 7.03 Hz, 2H), 6.75 (d, J = 6.59 Hz, 1H), 7.61 (d, J = 6.59 Hz, 1H).

[00693] *Part F: 1-Amino-N-((S)-1-(4-chloro-5-(4-cyano-3-fluorophenyl)-1H-imidazol-2-yl)-2-phenylethyl)-5,6,7,8-tetrahydroisoquinoline-6-carboxamide*: The product from Example 147 Part E (0.21 g, 0.67 mmol), Bop reagent (0.44 g, 1.0 mmol), and triethylamine (0.91 mL, 6.54 mmol) were added together with 15 mL of THF. The mixture was stirred at RT for 20 minutes under N_2 and the product from Part E of Example 120 (0.41 g, 0.90 mmol) was added. The resulting mixture was heated at 75 °C for 1 h under N_2. The reaction mixture was cooled and the solvent was removed. The residue was dissolved in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, and purified by flash chromatography (40 g silica, 0-15% MeOH in dichloromethane) to give 0.31 g of the desired product. LC/MS: 515.4, $(M+H)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.73 (dd, J = 12.96, 5.93 Hz, 1H), 2.10 (m, 1H) 2.39 (m, 1H), 2.58 (m, 4H), 3.22 (m, 2H), 5.24 (t, J = 7.69 Hz, 1H), 6.37 (d, J = 5.27 Hz, 1H), 7.23 (m, 5H), 7.64 (m, 3H,) 7.79(m, 1H).

[00694] *Part G: Chiral separation of the product from Part F*: The product from Example 147 Part F was separated by chiral prep-HPLC (OD column, 30% EtOH/MeOH (1:1) and 70% heptane with 0.15%DEA) to give diastereomer A and diastereomer B.

[00695] *Part H: (S)-1-Amino-5,6,7,8-tetrahydro-isoquinoline-6-carboxylic acid {(S)-1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenyl-ethyl}-amide*: Diastereomer A from Example 147 Part G (0.10 g, 0.19 mmol) and hydrazine (0.50 mL) were added together with 7 mL of n-butanol. The mixture was heated at 120 °C under N_2 for 1.5 h. The solvent was removed. The residue was purified by reverse phase HPLC to give 0.10 g of the desired product as the bis-TFA salt. LC/MS: 527.21, $(M+H)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.84 (m, 1H), 2.14 (m, 1H), 2.51 (m, 2H), 2.72 (m, 3H), 3.19 (m, 2H), 5.24 (m, 1H), 6.66 (d, J = 6.59 Hz, 1H), 7.24 (m, 5H), 7.49 (d, J = 8.35 Hz, 1H), 7.59 (d, J = 6.59 Hz, 1H) 7.69 (s, 1 H), 7.93 (d, J = 9.23 Hz, 1H).

Example 155

N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide, bis-trifluoroacetic acid salt

[00696] Example 155 was prepared by appropriate application of the procedures described for Example 120, where 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid instead of Boc-tranexamic acid was used in Example 120 Part F. MS: 512.2, $(M+H)^+$. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 3.17 (t, J = 6.37 Hz, 2H, 3.35 (m, 2H) 3.53 (t, J = 6.37 Hz, 2H), 4.41 (s, 2H), 5.41 (t, J = 7.91 Hz, 1H), 7.22 (m, 5H), 7.32 (d, J = 8.35 Hz, 1H), 7.50 (d, J = 10.11 Hz, 1H) 7.71 (m, 3H) 7.94 (d, J = 8.35 Hz, 1H).

Example 157

***trans*-4-Aminomethyl-cyclohexanecarboxylic acid {(S)-1-[5-(3-amino-1*H*-indazol-6-yl)-1*H*-imidazol-2-yl]-3-[(pyridin-2-ylmethyl)-carbamoyl]-propyl}-amide, tris-trifluoroacetic acid salt**

[00697] *Part A: (S)-2-Benzyloxycarbonylamino-pentanedioic acid 5-tert-butyl ester 1-[2-(4-cyano-3-fluoro-phenyl)-2-oxo-ethyl] ester*: (S)-2-Benzyloxycarbonylamino-pentanedioic acid 5-*tert*-butyl ester (674 mg, 2 mmol), Cs_2CO_3 (326 mg, 1 mmol) and DMF 5 mL) were stirred room temperature for 0.5 h. A solution of 1'-bromo-3-fluoro-4-cyanoacetophenone (484 mg, 2 mmol) in DMF (5 mL) was added. Stirring was continued for 16 h. The reaction mixture was diluted with EtOAc (100 mL). Three washings with a 10% LiCl solution, drying over MgSO4, filtration and removal of solvent in *vacuo* provided an orange oil (900 mg, 91% yield): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.77 (m, 3H), 7.35 (m, 5H), 5.52 (m, 1H), 5.42 (d, 1H, *J* = 16), 5.25 (d, 1H, *J* = 16), 5.11 (s, 2H), 4.60 (m, 1H), 2.45 (m, 2H), 1.44 (s, 9H); MS: 497 (M – H+)-.

[00698] *Part B: (S)-4-Benzyloxycarbonylamino-4-[5-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-butyric acid tert-butyl ester*: The intermediate from Example 157 Part A (900 mg, 1.81 mmol), NH_4OAc (1.54 g, 20 mmol) and xylenes (30 mL) were stirred at reflux temperature for 2.5 h. The reaction mixture was cooled to ambient temperature. Solvent was removed in *vacuo*. The residue was partitioned between EtOAc and a saturated Na_2CO_3 solution three times. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in *vacuo* to give a red orange oil. HPLC (0% to 100% EtOAc-hexanes) gave an orange oil (400 mg, 46% yield): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.3 (s, 1H), 7.59 (m, 4H), 7.35 (m, 5H), 5.83 (s, 1H), 5.13 (m, 2H), 4.79 (m, 1H), 2.53 (m,1H), 2.34 (m, 3H), 1.45 (s, 9H); MS: 477 (M – H+)-.

[00699] *Part C: (S)-4-Amino-4-[5-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-butyric acid tert-butyl ester*: The intermediate from Example 157 Part B (400 mg, 0.84 mmol), 10% Pd on C (40 mg) and EtOH (4 mL) were stirred under a hydrogen atmosphere for 2h. The reaction mixture was filtered through Celite. Solvent was removed in *vacuo* to give an oil. HPLC (0% to 10% MeOH-CH_2Cl_2) provided a pale yellow solid (189 mg, 65% yield): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.3 (s, 1H), 7.59 (m, 2H), 7.34 (1, 2H), 4.81 (t, 1H, J = 7), 2.59 (m, 2H), 2.28 (m, 2H), 1.42 (s, 9H); MS: 343 $(M - H^+)^-$.

[00700] *Part D: trans-(S)-4-{[4-(Benzyloxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}-4-[5-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-*

butyric acid tert-butyl ester: N-CBz-tranexamic acid (160 mg, 0.66 mmol), HOBt·H_2O (82 mg, 0.61 mmol), EDCI (117 mg, 0.61 mmol), (i-Pr)$_2$NEt (388 mg, 0.52 mL, 3 mmol) and DMF (1 mL) were stirred at room temperature for 15 min. A solution of the intermediate from Example 157 Part C (189 mg, 0.55 mmol) in DMF (1 mL) was added. Stirring was continued for 24 h. The reaction mixture was diluted with EtOAc (40 mL). The organic mix was washed with a 10% LiCl solution. Drying over $MgSO_4$, filtration and removal of solvent in *vacuo* afforded a tan solid (330 mg, 97% yield): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.1 (s, 1H), 7.60 (m, 1H), 7.35 (m, 2H), 6.97 (d, 1H, J = 8), 5.09 (s, 2H), 4.90 (d, 1H, J = 8), 4.81 (m, 1H), 3.06 (t, 2H, J = 7), 2.37 (m, 2H), 2.27 (m, 1H), 1.87 (m, 2H), 1.46 (s, 9H), 1.03 (m, 2H); HRMS (ES^+): Calcd for $C_{34}H_{41}FN_5O_5$: 618.3092, Found: 618.3098 $(M + H+)^+$.

[00701] *Part E: trans-(S)-4-{[4-(Benzyloxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}-4-[5-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-butyric acid*: The intermediate from Example 157 Part D (330 mg, 0.53 mmol), TFA (0.5 mL) and CH_2Cl_2 (0.5 mL) were stirred at ambient temperature for 2h. Solvent was removed in *vacuo* to give a tan solid (300 mg, 100% yield): ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 8.24 (m, 1H), 8.04 (s, 1H), 7.97 (m, 1H), 7.88 (d, 1H, J = 9), 7.81 (d, 1H, J = 9), 7.35 (m, 6H), 7.25 (m, 1H), 5.01 (s, 2H), 5.0 (m, 1H), 3.63 (m, 1H), 3.13 (m, 1H), 2.86 (m, 2H), 2.31 (m, 2H), 2.15 (m, 2H), 2.04 (m 1H), 1.75 (m, 2H), 1.27 (m, 5H), 0.88 (m, 1H); HRMS (ES^+): Calcd for $C_{30}H_{33}FN_5O_5$: 562.2466, Found: 562.2453 $(M + H)^+$.

[00702] *Part F: trans-(4-{(S)-1-[5-(4-Cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-3-[(pyridin-2-ylmethyl)-carbamoyl]-propylcarbamoyl}-cyclohexylmethyl)-carbamic acid benzyl ester*: The intermediate from the Example 157 Part E (325 mg, 0.53 mmol), HOBt·H_2O (81 mg, 0.6 mmol), EDC (115 mg, 0.6 mmol), (i-Pr)$_2$NEt (388 mg, 0.52 mL, 3.0 mmol) and DMF (1 mL) were stirred at room temperature under a nitrogen atmosphere for 15 min. 2-Aminomethylpyridine (65 mg, 0.6 mmol) was added, and stirring was continued for 88h. The reaction mixture was diluted with EtOAc (20 mL) and the organic mix was washed with a 10% LiCl solution (5 mL) three times. The organic layer was dried over $MgSO_4$ and filtered. Solvent was removed in *vacuo*. HPLC (0% to 10% MeOH-CH_2Cl_2) provided a pale yellow solid (40 mg, 12% yield): ^{1}H-NMR (MeOH-d_4, 400 MHz): δ 8.49 (m, 1H), 7.81 (t, 1H, J =

8), 7.73 (m, 2H), 7.35 (m, 11H), 5.08 (s, 1H), 4.50 (s, 2H), 3.37 (m, 4H), 2.98 (d, 2H, J = 7), 2.40 (m,2H), 2.25 (m, 2H), 1.86 (m, 6H), 1.47 (m, 2H), 1.05 (m, 2H); HRMS (ES^+): Calcd for $C_{36}H_{39}FN_7O_4$: 652.3048, Found: 652.3063 (M + H).

[00703] *Part G: trans-4-Aminomethyl-cyclohexanecarboxylic acid {(S)-1-[5-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-3-[(pyridin-2-ylmethyl)-carbamoyl]-propyl}-amide, tris-trifluoroacetic acid salt*: The intermediate from Example 157 Part F (98mg, 0.15 mmol) and a solution of HBr in acetic acid (33%, 3 mL) were stirred at ambient temperature for 21 h. Solvent was removed in *vacuo* to provide an oil. Reverse phase HPLC (0% to 100% CH_3CN-H_2O with 0.1% TFA) provided a white solid (20 mg, 39% yield): ^{1}H-NMR (MeOH-d_4, 400 MHz): δ 8.70 (d, 1H, J = 5), 8.38 (t, 1H, J = 8), 8.00 (s, 1H), 7.80 (m, 5H), 5.18 (t, 1H, J = 6), 4.93 (m, 5H), 4.69 (d, 1H, J = 16), 4.63 (d, 1H, J = 16), 2.78 (d, 2H, J = 7), 2.51 (m, 2H), 2.31 (m, 4H), 1.62 (m, 2H), 1.45 (m, 4H), 1.09 (m, 2H); HRMS (ES^+): Calcd for $C_{28}H_{33}FN_7O_2$: 518.2680, Found: 518.2698 (M + H).

[00704] *Part H: trans-4-Aminomethyl-cyclohexanecarboxylic acid {(S)-1-[5-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-3-[(pyridin-2-ylmethyl)-carbamoyl]-propyl}-amide, tris-trifluoroacetic acid salt*: The intermediate from Example 157 Part F (20 mg, 0.02 mmol), hydrazine hydrate (0.5 mL) and n-BuOH (0.5 mL) were heated in a microwave apparatus for 15 min at 120 °C. Solvent was removed in *vacuo* to provide a white solid (10 mg, 49% yield): ^{1}H-NMR (MeOH-d_4, 400 MHz): δ 8.48 (d, 1H, J = 2), 7.80 (t, 1H, J = 8), 7.67 (m, 2H), 7.35 (m, 4H), 5.11 (t, 1H, J = 7), 4.86 (m, 8H), 4.50 (s, 2H), 3.57 (t, 1H, J = 7), 2.81 (d, 2H, J = 7), 2.39 (m, 2H), 2.24 (m, 4H), 1.95 (m, 4H), 1.53 (m, 2H), 0.96 (t, 2H, J = 7); HRMS (ES^+): Calcd for $C_{28}H_{36}N_9O_2$: 530.2992, Found: 530.2991 (M + H)

Example 158

***trans*-4-Aminomethyl-cyclohexanecarboxylic acid {(S)-1-[5-phenyl-1*H*-imidazol-2-yl]-3-[(pyridin-2-ylmethyl)-carbamoyl]-ethyl}-amide**

[00705] This compound was prepared following the procedures described in Example 157, Parts A through H: ^{1}H-NMR (MeOH-d_4, 400 MHz): δ 8.30 (d, 1H, J = 8), 7.58 (d, 2H, J = 8), 7.43 (t, 1H, J = 8), 7.25 (m, 3H), 7.13 (m, 2H), 7.05 (d, 1H, J = 8), 5.40 (t, 1H, J = 7), 4.76 (m, 5H), 4.38 (d, 1H, J = 16), 4.30 (d, 1H, J = 16), 2.94

(dd, 1H, J = 15,7), 2.84 (dd, 1H, J = 15,7), 2.43 (d, 2H, J = 7), 2.10 (m, 1H), 1.77 (m, 4H), 1.34 (m, 4H), 0.89 (m, 1H); HRMS (ES^+): Calcd for $C_{26}H_{33}N_6O_2$: 461.2665, Found: 461.2657 (M + H).

Example 159

N-[2-(2S)-[2-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[[*trans*-[4-(aminomethyl)cyclohexanecarboxamido]ethyl]phenyl]-phenylacetamide, bis-trifluoroacetic acid salt

[00706] *Part A: trans-{4-[(S)-1-[4-(4-Cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-2-(2-nitro-phenyl)-ethylcarbamoyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester*: *L*-2-Nitro-N-(Boc)-phenylalanine (2.24 g, 7.23 mmol) was treated sequentially according to the procedures described in **Example 1** part A and Part B and **Example 2** part A to yield 3.0g (98 % yield) of the desired product. MS 450 $(M-H)^-$.

[00707] *Part B: trans- (4-{(S)-2-(2-Amino-phenyl)-1-[4-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-ethylcarbamoyl}-cyclohexylmethyl)-carbamic acid tert-butyl* ester: The product from **Example 159** Part A (284 mg, 0.48 mmol) was dissolved acetic acid (3.5 mL) and 5 drops of water. Iron powder (273 mg, 4.8 mmol) was added to the flask, and the reaction was heated to 50°C for 5 h. The reactions was cooled to rt, diluted with 50 mL of MeOH, and filtered through Celite. The solvents were removed in *vacuo* to yield 265 mg (98% yield) of the crude aniline. MS 559 (M-H)-.

[00708] *Part C: trans-{4-[(S)-1-[4-(4-Cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-2-(2-phenylacetylamino-phenyl)-ethylcarbamoyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester*: The product from **Example 159** Part B (132 mg, 0.23 mmol) and phenyl acetic acid (40 mg, 0.28 mmol) were dissolved in pyridine (0.7 mL, 0.71 mmol) and 1.5 mL of DMF. HOBt (45 mg, 0.3 mmol) and EDCI (60 mg, 0.30 mmol) were added to the flask, and the reaction was stirred at rt for 12 h. The reaction was diluted with EtOAc, extracted with ½ sat. brine (4-6 times), dried over $MgSO_4$, filtered and evaporated to dryness to yield the desired product 150 mg (95 % yield). MS 677 (M-H)-.

[00709] *Part E: trans-4-Aminomethyl-cyclohexanecarboxylic acid [(S)-1-[4-(4-cyano-3-fluoro-phenyl)-1H-imidazol-2-yl]-2-(2-phenylacetylamino-phenyl)-ethyl]-amide*: The product from **Example 159** part C (150 mg, 0.22 mmol) was treated under the condition described in **Example 2** part B and purified by prep HPLC (MeOH/H_2O/0.1 % TFA gradient) to yield 18 mg (14% yield) of the desired product. MS 577 (M-H)-.

[00710] *Part F: trans-4-Aminomethyl-cyclohexanecarboxylic acid [(S)-1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(2-phenylacetylamino-phenyl)-ethyl]-amide, bis trifluoroacetic acid* salt: The product from **Example 159** Part D (18 mg, 0.03 mol) was treated under the conditions described in **Example 120** Part H to yield 2.3 mg (11 % yield) of **Example 189**. 1H NMR (500 MHz, MeOH-d4) δ 0.93 - 1.11 (m, 1 H) 1.35 (ddd, *J*=58.97, 12.78, 3.57 Hz, 1 H) 1.48 - 1.62 (m, 1 H) 1.59 - 1.73 (m, 1 H) 1.74 - 1.92 (m, 2 H) 2.10 - 2.31 (m, 1 H) 2.76 (d, *J*=7.15 Hz, 1 H) 3.75 (q, *J*=13.75 Hz, 1 H) 5.24 (t, *J*=8.25 Hz, 1 H) 7.05 - 7.22 (m, 2 H) 7.26 - 7.33 (m, 1 H) 7.37 (t, *J*=6.60 Hz, 2 H) 7.63 (s, 1 H) 7.78 (s, 1 H) 7.88 (d, *J*=8.80 Hz, 1 H) HRMS m/z Calc'd for $C_{34}H_{39}N_8O_2$ $(M+H)^+$: 591.3196 Found 591.3221.

Example 162

(S)-4-(aminomethyl)-N-[1-[4-(4-amino-7-quinazolinyl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-*trans*-cyclohexanecarboxamide, bis-trifluoroacetic acid salt

[00711] *Part A: (4-{(S)-1-[4-(4-Amino-quinazolin-7-yl)-5-chloro-1H-imidazol-2-yl]-2-phenyl-ethylcarbamoyl}-cyclohexylmethyl)-carbamic acid tert-butyl ester*: The product from **Example 120** Part F (0.53 g, 0.9 mmol) and formamidine acetate (1.5 g, 14.4 mmol) were added together with 20 mL of DMAC. The mixture was heated at 140 °C under N_2 for 8 h. Additional formamidine (1.5 g, 14.4 mmol) was added, and the mixture was heated for additional 12 h. The mixture was cooled and water was added. The mixture was adjusted to pH 7 with aqueous $NaHCO_3$, and it was then extracted with EtOAc. The combined EtOAC extracts were washed with brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (120 g silica, 0-10% MeOH in CH_2Cl_2) to give 80 mg of the desired product. LC/MS: 604.1, 606.1, $(M+H)^+$.

with brine, dried over $MgSO_4$, filtered and evaporated to yield 420 mg (97 % yield) of a clear glass. MS 260 $(M+H)^+$.

[00715] *Part C: trans-2-{[4-(tert-Butoxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}-3-(3-difluoromethoxy-phenyl)-propionic acid ethyl ester*: The product from **Example 175** part B (420 mg, 1.62 mmol) was treated using the procedure described in **Example 2** part A to yield 800 mg (97% yields) of a white solid. MS 497$(M-H)^-$.

[00716] *Part D: trans-2-{[4-(tert-Butoxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}-3-(3-difluoromethoxy-phenyl)-propionic acid*: The product from **Example 175** part C (800 mg, 1.6 mmol) was treated accorded to the procedure described in **Example 26** to yield 750 mg of a white tacky solid. MS 469 (M-H+)-.

[00717] *Part E: trans-4-Aminomethyl-cyclohexanecarboxylic acid [1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(3-difluoromethoxy-phenyl)-ethyl]-amide, bis-trifluoroacetic acid salt*: The product from **Example 175** part D (284 mg, 0.6 mmol) was treated sequentially according to the procedures described in **Example 1** part A, **Example 2** Part B and **Example 120** Part H to yield 1.1 mg (9% yield) of the title compound as a clear glass after purification by prep HPLC. ^1H NMR (500 MHz, MeOH-d4) δ 0.98 - 1.20 (m, 1 H) 1.33 (s, 1 H) 1.49 - 1.65 (m, 1 H) 1.74 - 1.91 (m, *J*=11.55 Hz, 1 H) 2.25 (s, 1 H) 2.77 (d, *J*=7.15 Hz, 1 H) 3.16 (s, 1 H) 3.55 - 3.69 (m, 1 H) 5.34 (t, *J*=7.97 Hz, 1 H) 6.77 (s, 1 H) 7.00 (s, 1 H) 7.06 (dd, *J*=24.74, 8.25 Hz, 1 H) 7.33 (t, *J*=7.97 Hz, 1 H) 7.77 (d, *J*=8.25 Hz, 1 H) 7.84 (s, 1 H) 7.98 (d, *J*=8.80 Hz, 1 H); HRMS m/z Calc'd for $C_{27}H_{32}N_5O_3F_2$ $(M+H)^+$: 512.2473 Found 512.2485 .

Example 176

(S)-3-amino-N-[1-[4-[4-(carbamimidoyl)phenyl]-1H-imidazol-2-yl]-2-phenylethyl]-1H-indazole-5-carboxamide

[00718] *Part A: 4-[2-((S)-1-Amino-2-phenyl-ethyl)-1H-imidazol-4-yl]-benzonitrile dihydrochloride salt*: {(S)-1-[4-(4-Cyanophenyl)-1H-imidazol-2-yl]-2-phenylethyl}carbamic acid tert-butyl ester prepared as described in Ex. 28, Part A (1.0

[00712] *Part B: 4-Aminomethyl-cyclohexanecarboxylic acid {(S)-1-[4-(4-amino-quinazolin-7-yl)-5-chloro-1H-imidazol-2-yl]-2-phenyl-ethyl}-amide, bis-trifluoroacetic acid salt*: The product from **Example 162** Part A (80 mg, 0.13 mmol) was stirred with CH_2Cl_2 (5 mL) and TFA (2 mL) under N_2 for 0.5 h. The solvents were removed. The residue was purified by reverse phase HPLC to give 75 mg of the desired product as the bis-TFA salt. MS: 504.4, $(M+H)^+$. ^{1}H-NMR (400 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.34-1.47 (m, 2H), 1.55 (bs, 1H), 1.75-1.90 (m, 4H), 2.22 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.12-3.24 (m, 2H), 5.20 (m, 1H), 7.16-7.22 (m, 5H), 8.00 (m, 1H), 8.13 (s, 1H), 8.34 (m, 1H), 8.65 (s, 1H).

Example 175

N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-[3-(difluoromethoxy)phenyl]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide, bis-trifluoroacetic acid salt

[00713] *Part A: 2-(Benzhydrylidene-amino)-3-(3-difluoromethoxy-phenyl)-propionic acid ethyl ester*: N-(Diphenylmethylene) Glycine ethyl ester (500 mg, 1.87 mmol), Tetrabuylammonium Bromide (63 mg, 0.187 mmol) and 3-(Difluoromethoxy) benzyl bromide (0.5 mL, 1.87 mmol) were placed in a flask. The flask was evacuated and backfilled with argon. Anhyd dchloromethane was added to the flask, and the reaction was cooled in dry-ice acetone bath to -78°C. 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (0.7 mL, 2.44 mmol) was added slowly under argon at -78 °C. The reaction was allowed to stir at -78 °C for 30 minutes, and then warmed to room temperature over 16 h. The solvent was removed under vacuum. The residue was pre-adsorbed on to SiO_2 and the product was isolated via SiO_2 to yield 700 mg of light yellow oil. MS 424.0 (M+H) +.

[00714] *Part B: 2-Amino-3-(3-difluoromethoxy-phenyl)-propionic acid ethyl ester*: The product from **Example 175** Part A (700 mg, 1.65 mmol) was placed in a flask and dissolved in THF (30 mL). 30 % (w/v)Citric acid (aqueous solution, 30 mL) was added and the reaction was stirred at rt for 72 h. The solution was extracted with diethyl ether (50 mL), and the aqueous layer was adjusted to a pH 6 using a saturated $NaHCO_3$ solution. The aqueous solution was extracted with dichloromethane, washed

g, 2.57 mmol) was dissolved in dioxane (10 mL) and 4 N HCl in dioxane (10 mL) and an additional 5 mL dioxane were added. The resulting mixture was stirred for 2-2.5 h at room temperature under N_2, then diluted with ether. The resulting solid was triturated with additional ether and collected by filtration, washed with ether and hexane and dried to provide the amine dihydrochloride salt as a light green solid (0.89 g, 96%). ^{1}H NMR (500 MHz, DMSO-D6) δ 3.25 - 3.32 (m, 1 H) 3.33 - 3.40 (m, 1 H) 4.60 (s, 1 H) 7.11 (d, *J*=7.15 Hz, 2 H) 7.16 - 7.29 (m, 3 H) 7.78 - 7.89 (m, 3 H) 7.95 (d, *J*=8.25 Hz, 2 H) 8.65 (s, 2 H). m/z 289.2 $(M+H)^+$.

[00719] *Part B: 3-Cyano-N-{(S)-1-[4-(4-cyano-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-4-fluoro-benzamide*: A mixture of the compound of Example 176 Part A (100 mg, 0.28 mmol), 3-cyano-4-fluorobenzoic acid (46 mg, 0.28 mmol), triethylamine (0.085 mL, 0.61 mmol) and BOP (0.18 g, 0.4 mmol) in THF (5 mL) was stirred at rt overnight under N_2. Reaction mixture was diluted with water and extracted 3X with EtOAc. The combined extracts were washed with sat'd. $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4, filtered and evaporated. Chromatography on silica gel (hexane/EtOAc) provided the amide product (88 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.41 (dd, *J*=13.75, 7.15 Hz, 1 H) 3.58 (dd, *J*=13.47, 7.97 Hz, 1 H) 5.33 (q, *J*=7.70 Hz, 1 H) 7.01 - 7.09 (m, 1 H) 7.18 - 7.37 (m, 7 H) 7.66 (d, *J*=8.25 Hz, 2 H) 7.85 (d, *J*=8.25 Hz, 2 H) 7.89 - 7.96 (m, 1 H) 7.95 - 8.03 (m, 1 H) 9.74 (s, 1 H). m/z 436.1 $(M+H)^+$.

[00720] *Part C: 3-Amino-1H-indazole-6-carboxylic acid {(S)-1-[4-(4-cyano-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-amide*: The compound of Example 176 Part B (86 mg, 0.20 mmol) was dissolved in nBuOH (2 mL) and excess hydrazine (0.1 mL) was added. The mixture was heated in a sealed tube at 160 °C for 10 min using microwave irradiation. Reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc (2X). The combined extracts were washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The crude aminoindazole [m/z 448.1 $(M+H)^+$] was used without purification in the next step.

[00721] *Part D: N-3-Amino-1H-indazole-5-carboxylic acid {(S)-1-[4-(4-carbamimidoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-amide*: The compound of Example 176 Part C was dissolved in ethanol (8 mL) and the solution stirred in an ice

bath while HCl(g) was bubbled through the solution for 10-15 min. The flask was then tightly capped and kept in the refrigerator overnight. Flask was warmed to room temperature, and contents stirred for 3-4 h, then ethanol was evaporated. The resulting residue was triturated with ether to give a solid which was collected by filtration and dried in *vacuo*. The imidate thus obtained was redissolved in ethanol (5 mL) and excess ammonium carbonate (0.2 g) added. The mixture was stirred in a tightly capped flask for 48 h at room temperature. The reaction mixture was diluted with methanol, decanted and evaporated to dryness. The residue was redissolved in methanol and purified by prep C18 HPLC to provide the bis TFA salt of the title amidine product as an off-white solid (85 mg, 61%) after evaporation of solvents. ^{1}H NMR (500 MHz, DMSO-D6) δ 3.35 - 3.47 (m, 2 H) 5.51 (q, *J*=7.15 Hz, 1 H) 7.18 (t, *J*=7.15 Hz, 1 H) 7.21 - 7.34 (m, 6 H) 7.80 (d, *J*=8.80 Hz, 1 H) 7.89 (d, *J*=8.25 Hz, 2 H) 7.99 (d, *J*=8.80 Hz, 2 H) 8.03 - 8.15 (m, 1 H) 8.32 (s, 1 H) 8.94 (s, 1 H) 9.03 (s, 2 H) 9.31 (s, 2 H) 11.86 (s, 1 H). m/z 465.0 $(M+H)^+$.

Example 182

N-{(S)-1-[4-(4-Carbamimidoyl-phenyl)-1-ethyl-1H-imidazol-2-yl]-2-phenyl-ethyl}-benzamide

[00722] *Part A: N-{(S)-1-[4-(4-Cyano-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-benzamide*: The compound of **Example 176** Part A (0.15 g, 0.42 mmol) was coupled with benzoic acid using the procedure of **Example 176** Part B to provide the title compound (0.12 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 - 3.65 (m, 2 H) 5.34 (d, *J*=8.35 Hz, 1 H) 6.82 (d, *J*=7.47 Hz, 1 H) 7.19 - 7.35 (m, 7 H) 7.40 (t, *J*=7.69 Hz, 2 H) 7.45 - 7.56 (m, 1 H) 7.64 (d, *J*=7.03 Hz, 4 H) 7.86 (d, *J*=8.35 Hz, 2 H). m/z 393.1 $(M+H)^+$.

[00723] *Part B: N-{(S)-1-[4-(4-Cyano-phenyl)-1-ethyl-1H-imidazol-2-yl]-2-phenyl-ethyl}-benzamide*: The compound of **Example 182** Part A (60 mg, 0.15 mmol) was dissolved in DMF (2.5 mL) and potassium carbonate (32 mg, 0.23 mmol) was added followed by ethyl iodide (0.015 mL, 0.19 mmol), and the resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with water

and extracted with EtOAc (3X). The combined extracts were washed with water and brine, then dried over Na_2SO_4, filtered and evaporated. The residue was chromatographed on silica gel to provide the product (48 mg, 76%). ^{1}H NMR (400 MHz, DMSO-D6) δ 1.17 (t, J=7.25 Hz, 3 H) 3.34 - 3.48 (m, 2 H) 3.89 - 4.05 (m, 2 H) 5.46 (d, J=7.03 Hz, 1 H) 7.14 (d, J=7.03 Hz, 1 H) 7.21 (t, J=7.47 Hz, 2 H) 7.31 (d, J=7.47 Hz, 2 H) 7.41 (t, J=7.25 Hz, 2 H) 7.48 (d, J=7.03 Hz, 1 H) 7.76 - 7.84 (m, 3 H) 7.88 (s, 1 H) 7.94 (d, J=8.79 Hz, 2 H) 9.08 (d, J=8.35 Hz, 1 H). m/z 421.2 $(M+H)^+$.

[00724] *Part C: N-{(S)-1-[4-(4-Carbamimidoyl-phenyl)-1-ethyl-1H-imidazol-2-yl]-2-phenyl-ethyl}-benzamide*: The compound of **Example 182** Part B (17 mg) was dissolved in ethanol (2 mL) and hydroxylamine hydrochloride (15 mg, 5 eq) and triethylamine (0.03 mL, 5 eq) were added. The mixture was heated in a sealed tube at 125 °C for 15 min using microwave irradiation. Additional aliquots of hydroxylamine hydrochloride and triethylamine were added and microwave irradiation repeated for an additional 10 min at 120 °C. Solvent was evaporated, and the residue redissolved in acetic acid (2 mL) and treated with acetic anhydride (0.015 mL, 3 eq). The solution was stirred for 15 min at room temperature followed by addition of zinc dust (25 mg, 10 eq) and a little MeOH. Mixture was then stirred overnight at room temperature. The reaction was filtered through a pad of Celite and solids washed with MeOH. Filtrate was evaporated, and residue purified by prep C18 HPLC to provide the bis-TFA salt of the title compound as a white solid (16 mg, 60%). ^{1}H NMR (400 MHz, DMSO-D6) δ 1.20 (t, J=7.03 Hz, 3 H) 3.33 - 3.52 (m, 2 H) 3.93 - 4.10 (m, 2 H) 5.49 (d, J=7.47 Hz, 1 H) 7.16 (t, J=7.47 Hz, 1 H) 7.23 (t, J=7.25 Hz, 2 H) 7.32 (d, J=7.03 Hz, 2 H) 7.43 (t, J=7.47 Hz, 2 H) 7.51 (t, J=7.47 Hz, 1 H) 7.84 (dd, J=7.69, 5.49 Hz, 4 H) 7.95 (s, 1 H) 8.00 (d, J=8.35 Hz, 2 H) 8.92 (s, 2 H) 9.12 (d, J=7.91 Hz, 1 H) 9.25 (s, 2 H). m/z 450.2 $(M+H)^+$.

Example 183

N1-{(S)-1-[4-(4-Carbamimidoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-2-fluoro-terephthalamide

[00725] *Part A: ((S)-1-{4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-1H-imidazol-2-yl}-2-phenyl-ethyl)-carbamic acid tert-butyl ester*: {(S)-1-[4-(4-

Cyanophenyl)-1H-imidazol-2-yl]-2-phenylethyl}carbamic acid tert-butyl ester prepared as described in **Example 28** Part A (1.00 equiv; 2.57 mmoles; 1.00 g) was dissolved in 15 mL EtOH and Hydroxylamine Hydrochloride (12.87 mmoles; 894.42 mg) and Triethylamine (12.87 mmoles; 1.79 mL) were added. The resulting solution was heated at reflux in an 80 °C oil bath under N_2 overnight. Reaction was cooled to room temperature and evaporated to remove EtOH. Residue was suspended in a mixture of EtOAc/EtOH (~10:1) and filtered to remove inorganic solids. Filtrate was reconcentrated to a yellow foam. This residue was redissolved in 10 mL HOAc and treated with stirring under N_2 with Acetic Anhydride (4.23 mmoles; 400 µL). Solution was stirred for 20 min at room temperature, then heated in 80 °C oil bath for 2h, cooled to room temperature and stirred overnight. Most of HOAc was removed on rotary evaporator, then residue was diluted with water and carefully neutralized by addition of sat'd $NaHCO_3$ to pH ~8. Extracted 3X with CH_2Cl_2. Combined extracts were washed with brine then dried over $MgSO_4$, filtered and evaporated to a lt red foam. Residue was purified on silica gel to provide the product as a lt pinkish tan foam. (590 mg; 51.4%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9 H) 2.65 (s, 3 H) 3.28 - 3.44 (m, 2 H) 4.88 (d, J=7.70 Hz, 1 H) 5.23 (s, 1 H) 7.13 - 7.36 (m, 5 H) 7.42 - 7.55 (m, 1 H) 7.88 (d, J=8.25 Hz, 2 H) 8.06 (d, J=8.25 Hz, 2 H) 9.67 (s, 1 H). m/z 446.1 $(M+H)^+$.

[00726] *Part B: (S)-1-{4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-1H-imidazol-2-yl}-2-phenyl-ethylamine dihydrochloride*: The BOC group was removed from the compound of **Example 183** Part A using procedure of Ex. 176, Part A to provide the hydrochloride salt of the amine as a tan solid in 46% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (s, 3 H) 2.87 (dd, J=13.75, 9.35 Hz, 1 H) 3.44 (dd, J=13.75, 4.40 Hz, 1 H) 4.44 (dd, J=9.35, 4.40 Hz, 1 H) 7.20 - 7.31 (m, 5 H) 7.34 (t, J=7.42 Hz, 3 H) 7.85 (s, 1 H) 8.08 (d, J=8.80 Hz, 2 H). m/z 346.0 $(M+H)^+$, 330.0 $(M+H-NH3)^+$.

[00727] *Part C: 4-Cyano-2-fluoro-N-((S)-1-{4-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-1H-imidazol-2-yl}-2-phenyl-ethyl)-benzamide*: The compound of **Example 183** Part B was coupled to 4-cyano-2-fluorobenzoic acid using the procedure of **Example 176** Part B to provide the amide in 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.64 (s, 3 H) 3.43 (dd, *J*=13.75, 7.15 Hz, 1 H) 3.58 (dd, *J*=13.75,

7.70 Hz, 1 H) 5.38 (q, *J*=7.15 Hz, 1 H) 7.20 - 7.33 (m, 7 H) 7.42 (d, *J*=9.90 Hz, 1 H) 7.54 (d, *J*=8.25 Hz, 2 H) 7.86 (s, 1 H) 8.05 (d, *J*=8.25 Hz, 2 H) 8.14 (t, *J*=7.70 Hz, 1 H) 9.43 (s, 1 H). m/z 493.1 $(M+H)^+$.

[00728] *Part D: 2-Fluoro-N1-((S)-1-{4-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-1H-imidazol-2-yl}-2-phenyl-ethyl)-terephthalamide*: A mixture of the compound of **Example 183** Part C (75 mg, 0.15 mmol), potassium carbonate (66 mg, 3 eq) and 30% hydrogen peroxide (0.055 mL, 11 eq) in DMSO (2.5 mL) was stirred at room temperature under N_2 overnight. Reaction mixture was diluted with water and EtOAc, and phases separated. Aqueous phase was reextracted with EtOAc (2X). Combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting crude amide was used without purification. m/z 511.0 $(M+H)^+$.

[00729] *Part E: N1-{(S)-1-[4-(4-Carbamimidoyl-phenyl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-2-fluoro-terephthalamide*: The compound of **Example 183** Part D (68 mg) and 10% Pd/C (35 mg, wet, Degussa) were suspended in a mixture of methanol and triethylamine (4.5 ml, 8:1) and stirred under 1 atm H_2 overnight. Catalyst was removed by filtration through Celite and washed with MeOH. Filtrate was evaporated and residue purified by prep C18 HPLC to provide the bis TFA salt of the title compound as a white solid (48 mg, 53%). 1H NMR (500 MHz, DMSO-D6) δ ppm 3.23 - 3.31 (m, 1 H) 3.41 (dd, J=13.75, 6.60 Hz, 1 H) 5.43 (q, J=7.70 Hz, 1 H) 7.13 - 7.23 (m, 1 H) 7.23 - 7.31 (m, 5 H) 7.59 - 7.66 (m, 2 H) 7.67 - 7.77 (m, 2 H) 7.87 (t, J=7.70 Hz, 2 H) 7.99 (d, J=8.25 Hz, 3 H) 8.13 (s, 1 H) 8.95 (s, 2 H) 8.98 - 9.06 (m, 1 H) 9.27 (s, 2 H). m/z 471.0 $(M+H)^+$.

Example 188

N1-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-2-fluoroterephthalamide, bis-trifluoroacetic acid salt

[00730] **Example 188** was prepared similarly by appropriate application of the procedures described for **Example 120**, where 4-carbamoyl-2-fluorobenzoic acid instead of Boc-tranexamic acid was used in **Example 120** Part F. ^{1}H-NMR (500 MHz, DMSO-d6) δ 3.16 (dd, J = 13.75, 8.80 Hz, 1H), 3.30 (dd, J = 13.75, 6.05 Hz, 1H) 5.31-5.43 (m, 1H), 7.16-7.23 (m, 1H), 7.25-7.31 (m, 5H), 7.38 (d, J = 8.80 Hz,

1H), 7.55 (t, J = 7.42 Hz, 1H), 7.62 (d, J = 5.50 Hz, 2H), 7.65-7.76 (m, 2H), 7.86 (d, J = 8.80 Hz, 1H), 8.12 (s, 1H), 8.97 (d, J = 8.25 Hz, 2H), 12.05 (s, 1H), 12.81 (s, 1H).

Example 189

N1-((S)-1-(4-(4-aminoquinazolin-7-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-2-fluoroterephthalamide, bis-trifluoroacetic acid salt

[00731] Example 189 was prepared by appropriate application of the procedures for Example 162, excluding Example 162 Part G and using 4-carbamoyl-2-fluorobenzoic acid instead of Boc-tranexamic acid in the procedure from Example 120 Part F . MS: 530.01 , $(M+H)^+$. ^{1}HNMR (500 MHz, DMSO-d_6) δ 3.14-3.24 (m, 1H), 3.25-3.35 (m, 1H,) 5.31-5.44 (m, 1H), 7.15-7.24 (m, 1H), 7.24-7.33 (m, 5H), 7.54 (t, J = 7.70 Hz, 1H), 7.64 (s, 1H), 7.66-7.76 (m, 3H), 7.99 (d, J = 8.80 Hz, 1H), 8.13 (s, 2H), 8.46 (d, J = 8.80 Hz, 1H), 8.80 (s, 1H), 9.07 (d, J = 6.60 Hz, 1H), 13.20 (s, 1H).

Example 190

1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-5,6,7,8-tetrahydroisoquinoline-6-carboxamide, bis-trifluoroacetic acid salt

[00732] Example 190 was similarly prepared by appropriate application of the procedures for Example 147 Part H using the diastereomer B from Part G of Example 147 . ^{1}H-NMR (400 MHz, d_4-MeOH) δ 1.75 (dd, J = 13.40, 10.33 Hz, 1H), 2.01 (m, 1H), 2.45 (t, J = 6.37 Hz, 2H), 2.73 (m, 1H), 2.90 (m, 2H), 3.20 (m, 2H), 5.28 (m, 1H), 6.69 (d, J = 6.59 Hz, 1H), 7.25 (m, 5H), 7.51 (d, J = 8.79 Hz, 1H), 7.59 (d, J = 6.59 Hz, 1H), 7.71 (s, 1H), 7.95 (d, J = 8.79 Hz, 1H).

Example 191

1-amino-N-((S)-1-(4-(4-aminoquinazolin-7-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-5,6,7,8-tetrahydroisoquinoline-6-carboxamide, bis-trifluoroacetic acid salt

[00733] Example 191 was prepared using the product from Part F of Example 147 by appropriate application of the procedures described in Part A of Example 162.

LC/MS: 539.2 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 1.77 (m, 1H), 2.00 (d, J = 3.95 Hz, 1H,) 2.45 (m, 2H), 2.74 (m, 2H,) 2.91 (m, 1H), 3.21 (m, 2 H), 5.26 (m, 1H), 6.67 (t, J = 7.25 Hz, 1H), 7.23 (m, 5H), 7.59 (t, J = 6.59 Hz, 1H), 8.02 (m, 1 H), 8.16 (d, J = 4.39 Hz, 1H), 8.36 (dd, J = 8. 79 and 1.76 Hz, 1H), 8.65 (s, 1H).

Example 192

1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-3-methylisoquinoline-6-carboxamide, bis-trifluoroacetic acid salt

[00734] *Part A: (Z)-3-(3-Bromophenyl)-2-methylacrylic acid*: 3-Bromobenziladelhyde (2.6 g, 0.014 mol) and (carbethoxyethylidene)triphenylphosphorane (5.6 g, 0.015 mol) were added together with 30 mL of toluene. The mixture was stirred at RT under N_2 for 24 h. The solvent was removed. The residue was dissolved in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica, Hexane/EtOAc) to give 3.7 g of the desired ester. MS: 271.2/273.2 $(M+1)^+$. The ester was then dissolved in 30 mL of THF and 10 mL of water. LiOH (1.32 g, 0.031 mol) was added. The mixture was stirred at RT under N_2 for 72 h. The THF was removed. The resulting mixture was diluted with water and extracted with EtOAc (discarded). The aqueous mixture was acidified with HCl and extracted with EtOAc. This EtOAc extract was washed with brine, dried over $MgSO_4$ and concentrated to a white solid (3.2 g). ^{1}HNMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 7.29 (m, 2H), 7.47 (d, J = 7.91 Hz, 1H), 7.56 (s, 1H), 7.73 (s, 1H).

[00735] *Part B: 6-Bromo-3-methylisoquinolin-1(2H)-one*: The product from **Example 192** Part A (2.76 g, 11.45 mmol) and triethylamine (3.60 mL, 22.90 mmol) were added together with 18 mL of acetone. The mixture was cooled to 0 °C, followed by the dropwise addition of ethyl chloroformate (1.85 mL, 17.17 mmol). The reaction mixture was stirred at 0-5 °C under N_2 for 1h. To it was added the slurry of sodium azide (1.34g, 20.60 mmol) in 2 mL of water. The reaction mixture was stirred at rt under N_2 overnight. The solvent was removed. The residue was dissolved in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, and dried in *vacuo* to give 3.4 g of 80% pure desired acyl azide. A solution of

tributylamine (4.40mL, 18.49 mmol) and diphenylmethane (15mL) was heated to 190 C . To it was added dropwise the solution of the acyl azide (3.4 g of 80% pure material, 10.3 mmol) in diphenylmethane (12 mL) over 12 minutes. The mixture was stirred at 220 °C for 2 h under N_2. It was cooled to RT. The crude product was precipitated and filtered. It was purified by flash chromatography (120 g silica, 0-10% MeOH in dichloromethane) to give 0.43 g of the desired product. MS: 238.2, 240.1 $(M+1)^+$. ^{1}HNMR (400 MHz, DMSO-d_6) δ 2.20 (s, 3H), 6.30 (s, 1H), 7.52 (d, J = 8.79 Hz, 1H), 7.80 (s, 1H), 7.81 (d, J = 8.35 Hz, 1H).

[00736] *Part C: 6-Bromo-3-methylisoquinolin-1-amine*: Phosphorus oxychloride (2.5 mL) was cooled in an ice-bath and was then added dropwise to the product from **Example 192** Part B (120 mg, 0.5 mmol). The mixture was heated to 110 °C under N_2 for 1.5 h. The reaction was cooled, and quenched with water and MeOH. More water was then added. The solid was filtered and washed with 1N NaOH and water to give 115 mg of solid. The solid obtained (51 mg) was combined with 1 mL of 13-15% NH_3 in ethylene glycol. The mixture was heated in a sealed tube via microwave irradiation at 170 °C for 20 minutes. The reaction was cooled and water was added. The solid was filtered and purified by ISCO flash chromatography (silica, CH_2Cl_2/MeOH) to give 12 mg of the desired product. MS: 237.1/239.1 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 2.39 (s, 3H), 6.76 (s, 1H), 7.53(m, 1H), 7.81 (d, J = 1.76 Hz, 1H), 7.98 (d, J = 8.79 Hz, 1H).

[00737] *Part D: 1-Amino-3-methylisoquinoline-6-carbonitrile*: The product from **Example 192** Part C (22 mg, 0.093 mmol), $Zn(CN)_2$ (12 mg), and $Pd(PPh_3)_4$ (8 mg) were added with 2 mL of DMF. The mixture was heated in a sealed tube in a microwave at 180 °C for 10 minutes. The mixture was filtered and washed with EtOAc. The filtrate was concentrated, and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to give 12 mg of the desired product. LC/MS: 184.18 $(M+1)^+$.

[00738] *Part E: 1-amino-3-methylisoquinoline-6-carboxylic acid*: The product from **Example 192** Part D (35 mg) was added with 4 mL of MeOH and 4 mL of 15% aqueous NaOH. The mixture was heated at 70-85 °C for 2 h. It was concentrated, acidified with HCl and TFA to pH = 5. The solid was filtered and purified by reverse phase prep-HPLC to give 18 mg of the TFA salt. LC/MS: 203.03 $(M+1)^+$.

[00739] *Part F: 1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl)-2-phenylethyl)-3-methylisoquinoline-6-carboxamide, bis-trifluoroacetic acid salt*: The product from **Example 192** Part E and the product from Part E of **Example 120** were coupled and then converted to the aminoindazole using the methods described in **Example 120** Part F and Part H, respectively. MS: 537.0 $(M+1)^+$. ^{1}HNMR (400 MHz, d_4-MeOH) δ 2.52 (s, 3H), 3.41 (m, 2H), 5.46 (t, J = 7.91 Hz, 1H), 7.05 (s, 1H), 7.23 (m, 5H), 7.50 (d, J = 8.79 Hz, 1H) 7.71 (s, 1 H), 7.98 (m, 2H), 8.19 (s, 1H), 8.43 (d, J = 8.79 Hz, 1H).

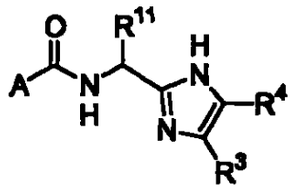
Example 200

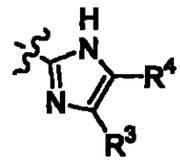
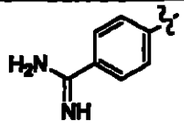
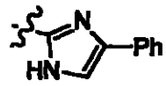
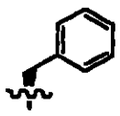
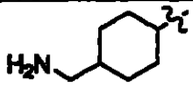
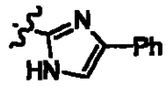
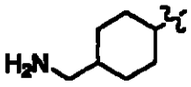
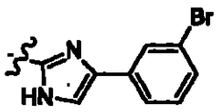
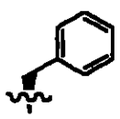
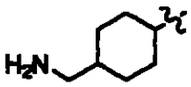
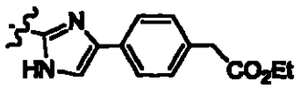
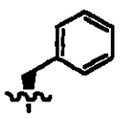
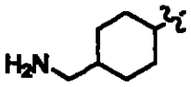
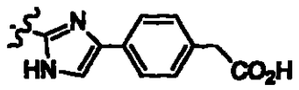
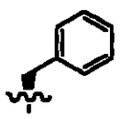
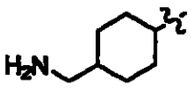
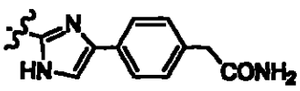
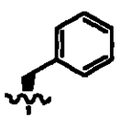
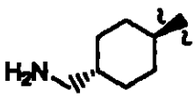
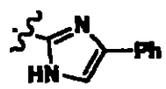
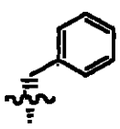
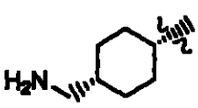
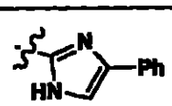
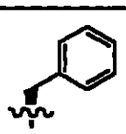
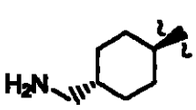
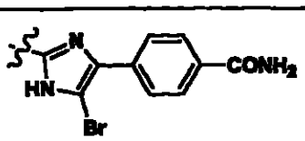
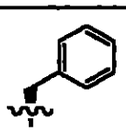
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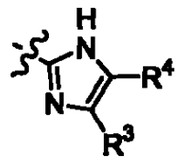
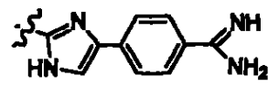
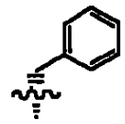
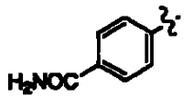
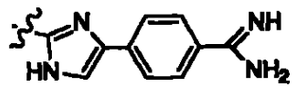
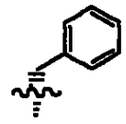
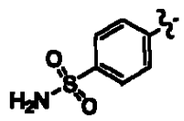
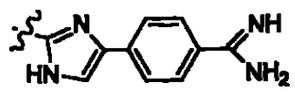
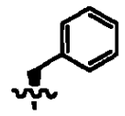
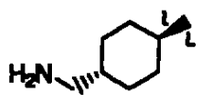
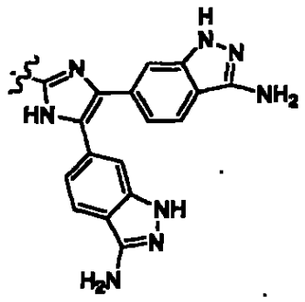
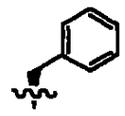
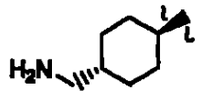
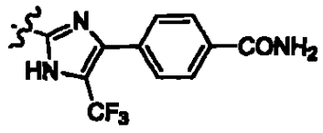
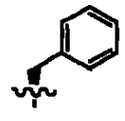
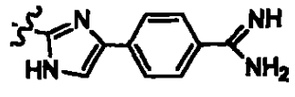
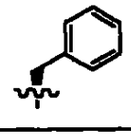
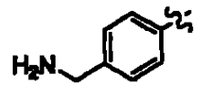
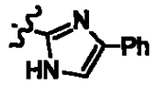
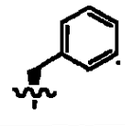
[00740] This compound was prepared following the procedures described in **Example 120**: ^{1}H NMR (500 MHz, Solvent) δ 0.90 - 1.01 (m, 2 H), 1.18 - 1.24 (m, 2 H), 1.42 - 1.50 (m, 1 H), 1.50 - 1.62 (m, 2 H), 1.68 - 1.79 (m, 2 H), 2.00 - 2.09 (m, 1 H), 2.71 (d, *J*=7.15 Hz, 2 H), 2.94 (dd, *J*=13.00, 8.80 Hz, 2 H), 3.02 (dd, *J*=13.00, 6.04 Hz, 2 H), 3.13 (dd, *J*=15.12, 10.17 Hz, 1 H), 4.57 - 4.65 (m, 1 H), 7.18 - 7.23 (m, 1 H), 7.26 - 7.30 (m, 4 H), 7.47 (d, *J*=9.90 Hz, 1 H), 7.74 (s, 1 H) 7.89 (s, 1 H), 7.97 (d, *J*=8.25 Hz, 1 H). HRMS (ES^+): Calcd for $C_{27}H_{33}N_7O$: 471.2747, Found: 472.2839 (M + H).

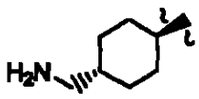
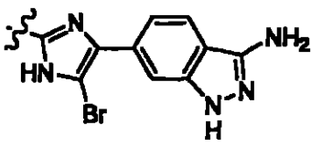
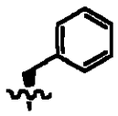
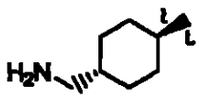
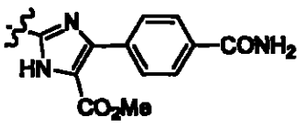
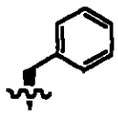
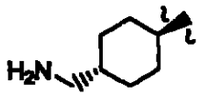
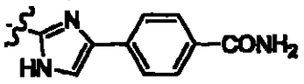
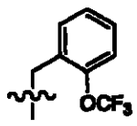
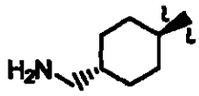
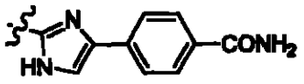
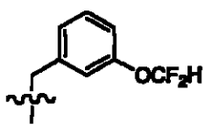
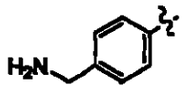
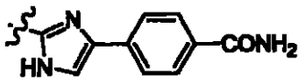
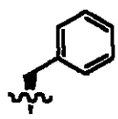
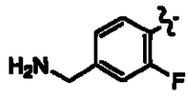
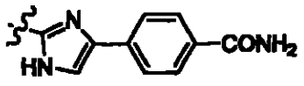
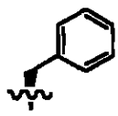
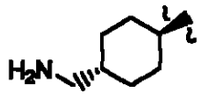
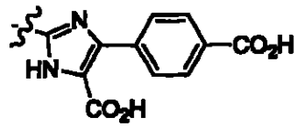
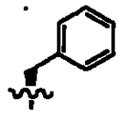
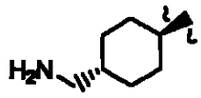
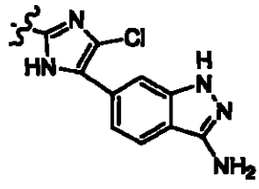
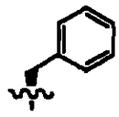
[00741] Tables 1-6 below summarize the prepared examples of compounds in the present invention.

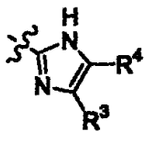
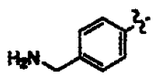
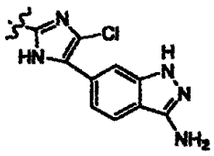
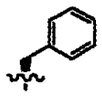
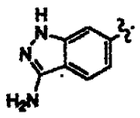
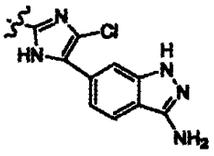
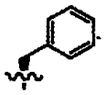
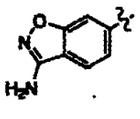
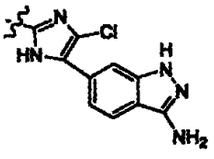
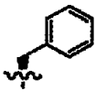
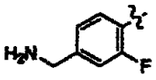
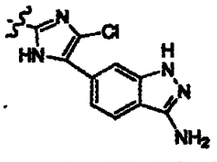
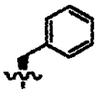
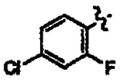
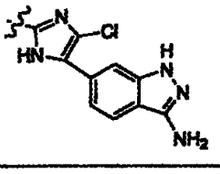
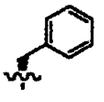
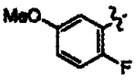
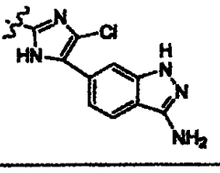
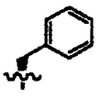
Table 1

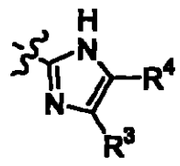
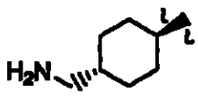
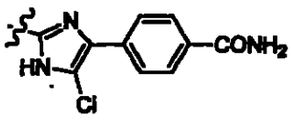
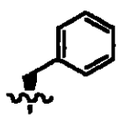
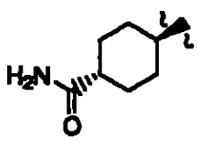
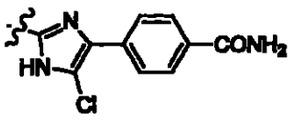
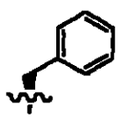
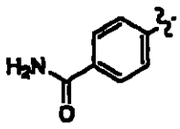
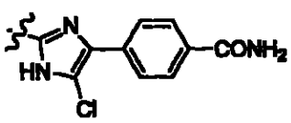
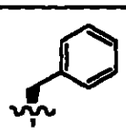
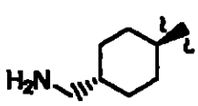
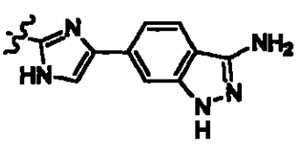
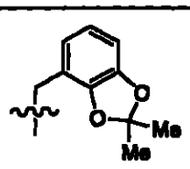
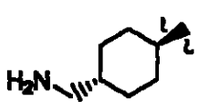
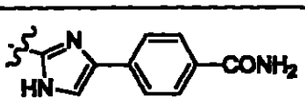
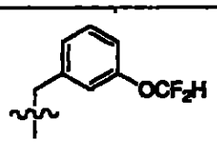
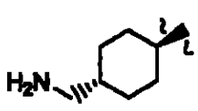
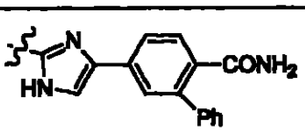
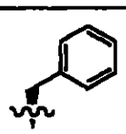
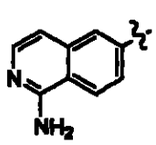
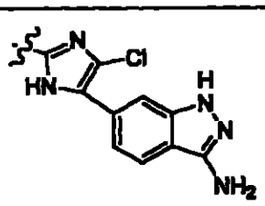
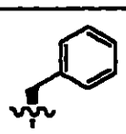
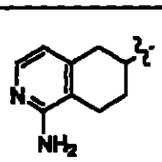
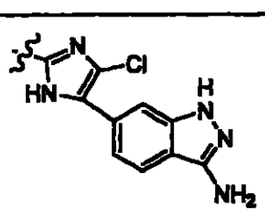
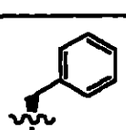


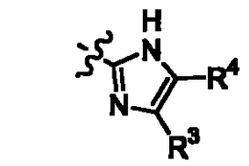
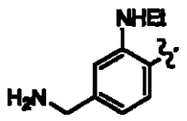
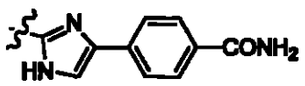
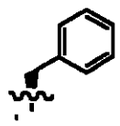
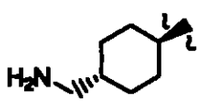
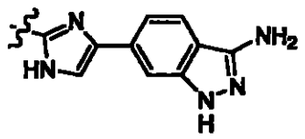
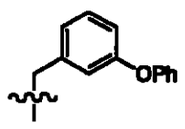
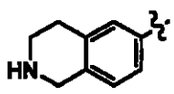
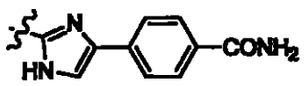
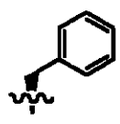
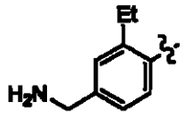
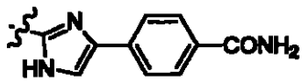
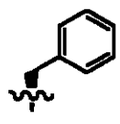
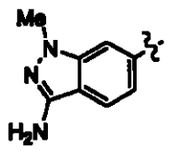
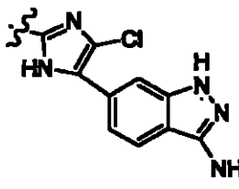
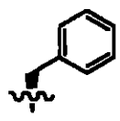
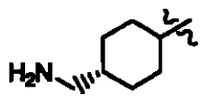
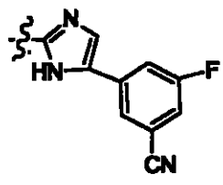
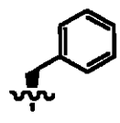
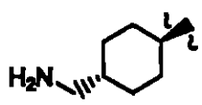
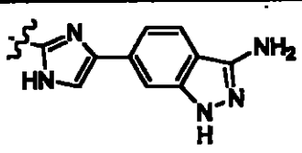
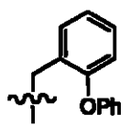
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
1				410.20
14				417.27
15				483.07, 481.07
25				489.29
26				461.26
27				460.27
75				403.2
76				403.1
82				526.1, 524.1

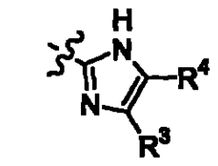
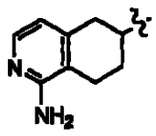
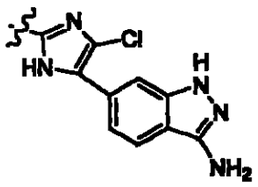
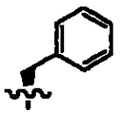
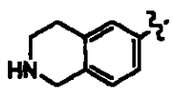
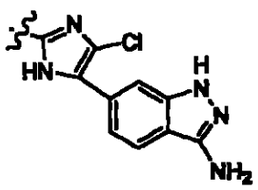
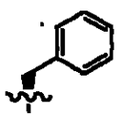
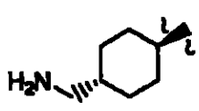
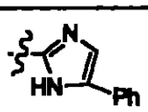
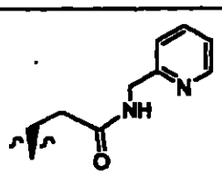
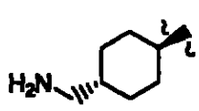
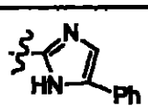
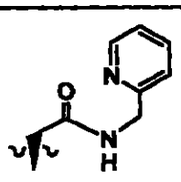
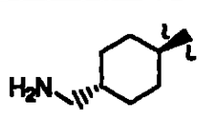
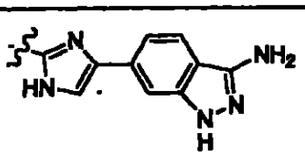
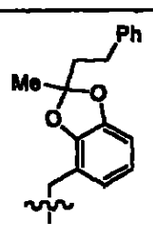
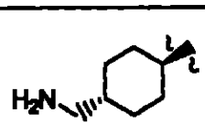
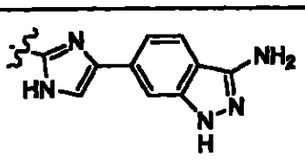
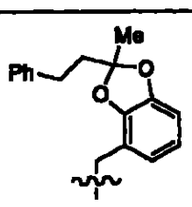
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
83				410.2
84				453.2
86				489.2
106				589.5
107				514.2
108				410.2
112				397.4

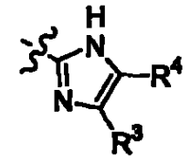
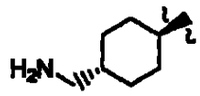
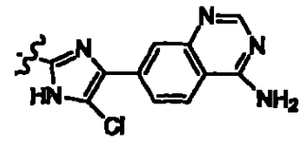
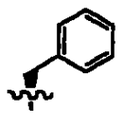
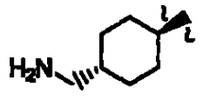
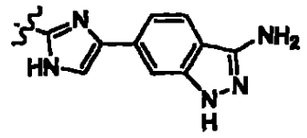
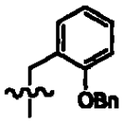
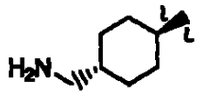
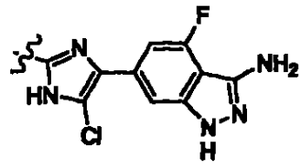
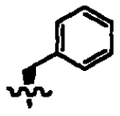
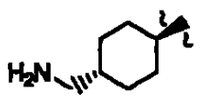
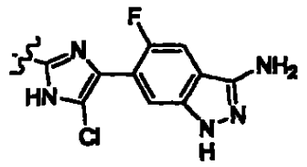
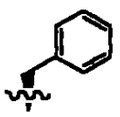
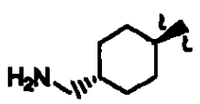
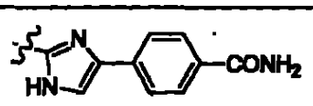
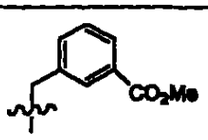
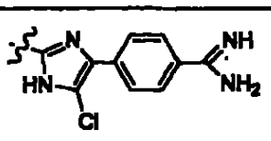
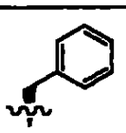
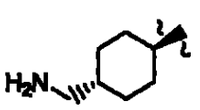
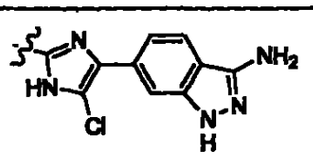
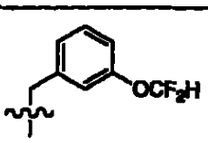
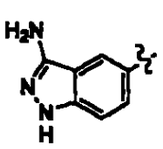
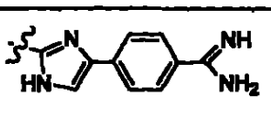
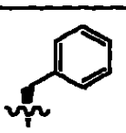
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
113				538.4
114				504.4
115				530.2
116				512.3
117				440.2
118				458.2
119				491.2
120				492.4

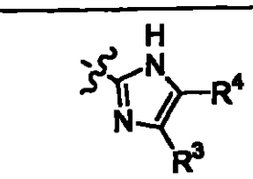
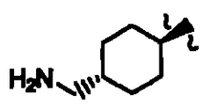
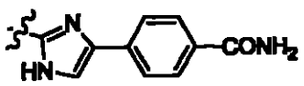
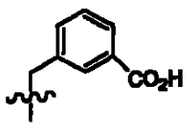
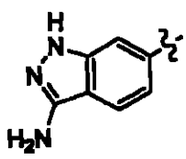
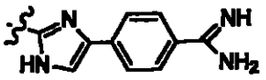
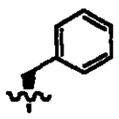
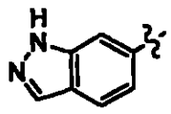
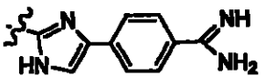
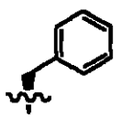
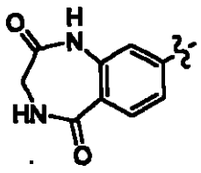
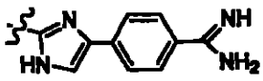
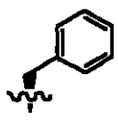
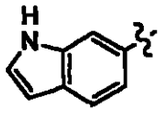
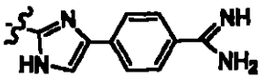
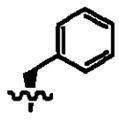
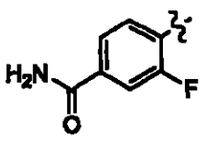
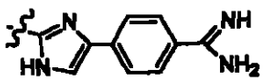
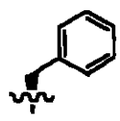
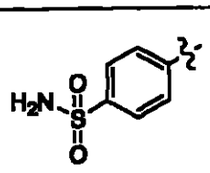
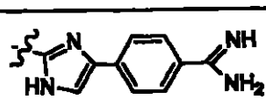
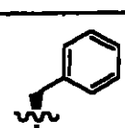
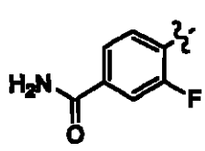
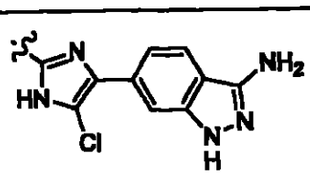
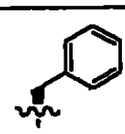
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
121				486.3
122				510.3 (M-H+)-
123				513.1
124				504.1
128				509.3
129				505.3

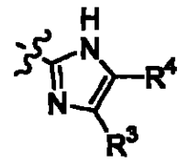
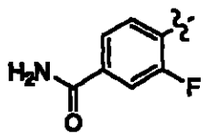
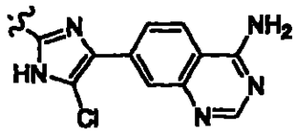
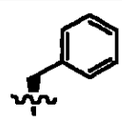
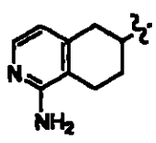
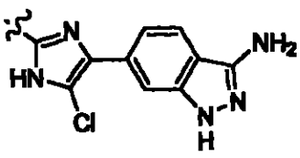
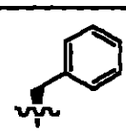
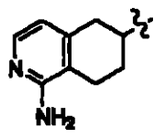
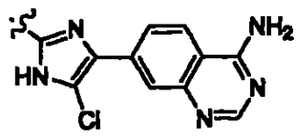
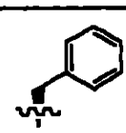
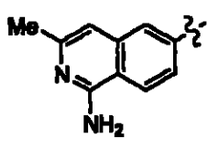
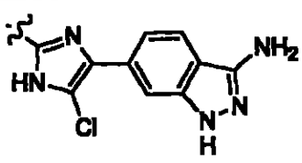
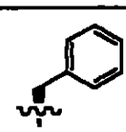
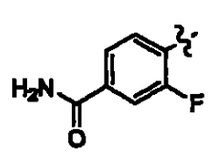
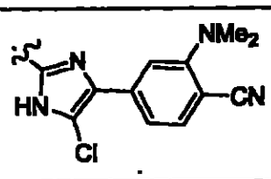
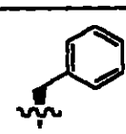
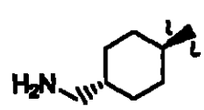
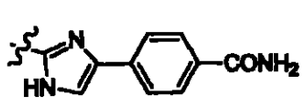
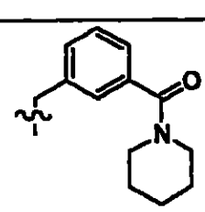
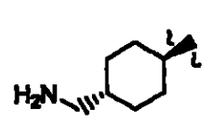
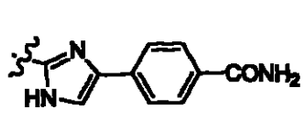
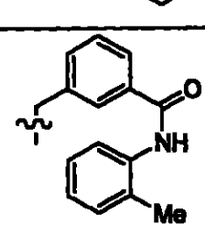
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
130				480.4
131				506.2
132				500.1
133				530.3
134				512.1
135				522.4
136				523.2
137				527.3

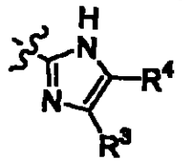
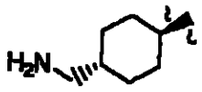
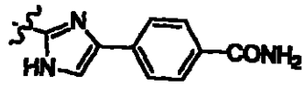
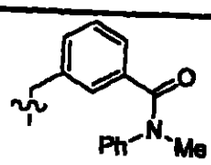
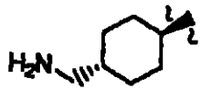
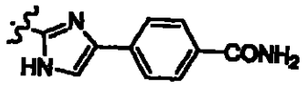
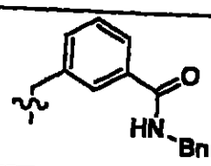
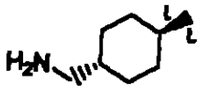
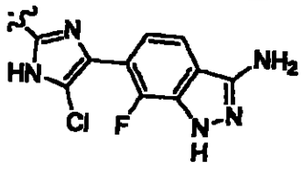
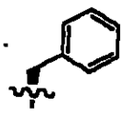
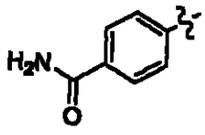
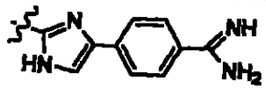
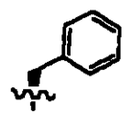
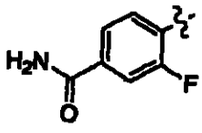
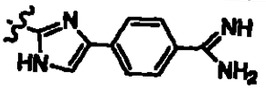
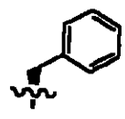
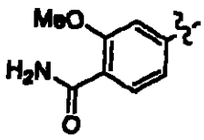
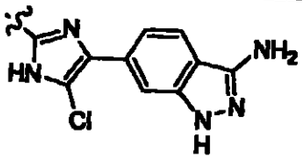
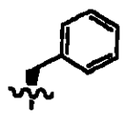
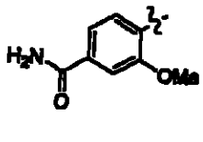
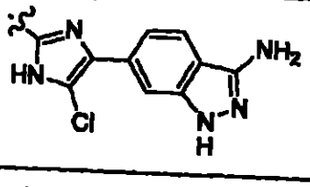
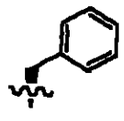
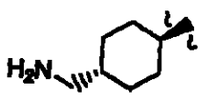
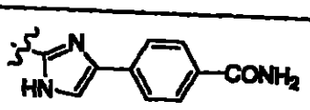
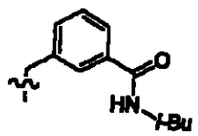
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
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141				550.3
142				466.2
143				468.4
144				526.3
145				446.3
146				550.2

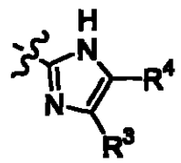
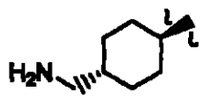
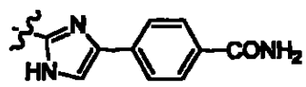
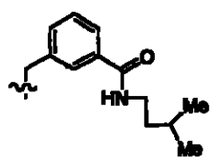
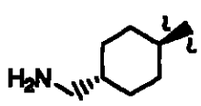
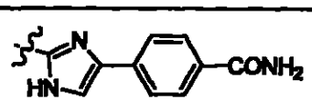
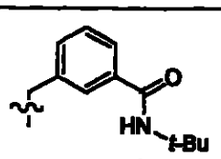
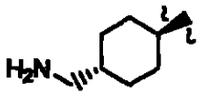
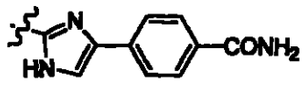
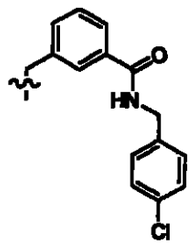
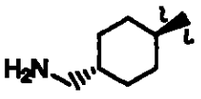
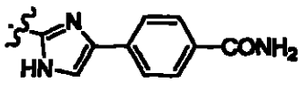
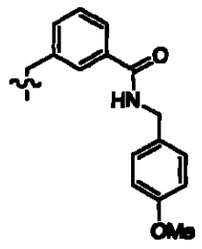
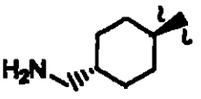
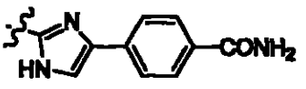
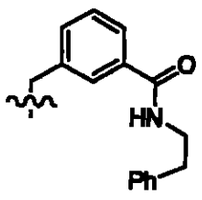
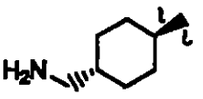
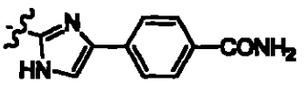
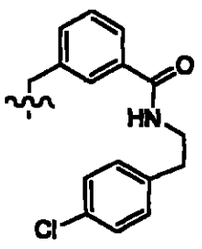
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
147				527.3
155				512.2
157				530.3
158				461.3
160				620.3
161				620.3

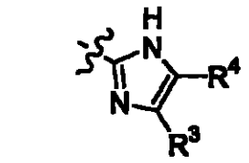
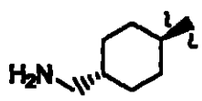
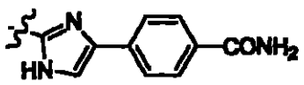
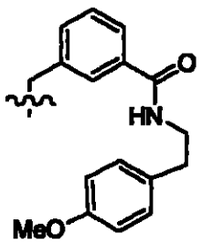
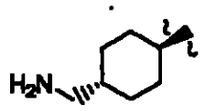
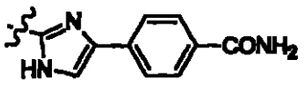
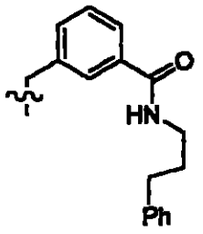
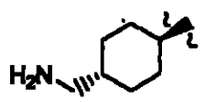
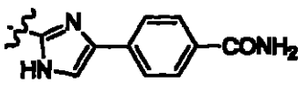
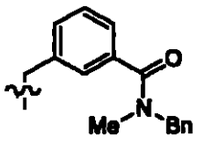
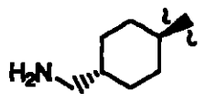
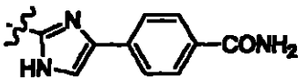
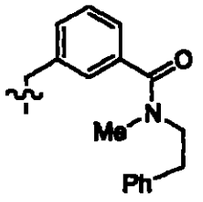
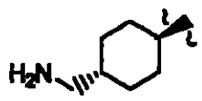
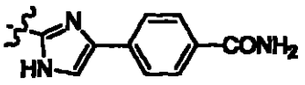
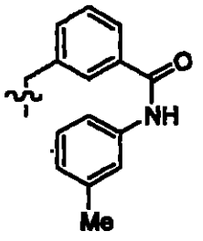
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
162				504.2
165				564.0
171				510.3
172				510.3
173				504.1
174				442.2
175				558.2
176				465.0

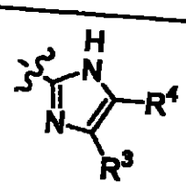
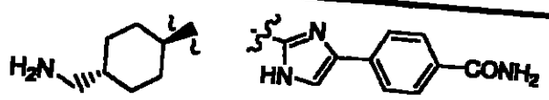
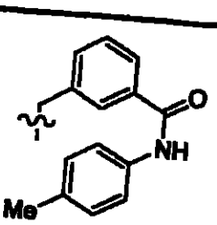
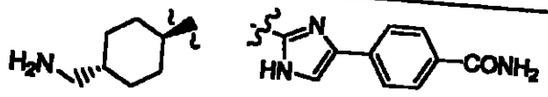
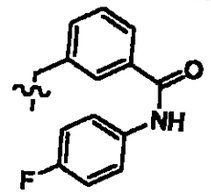
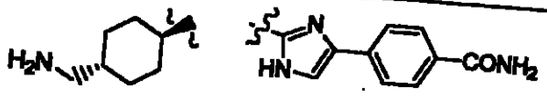
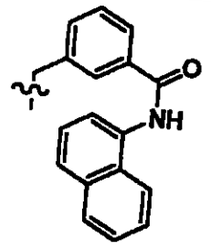
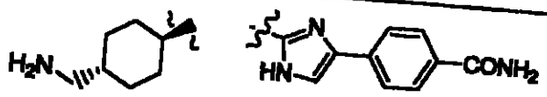
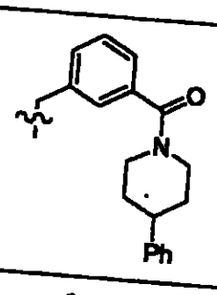
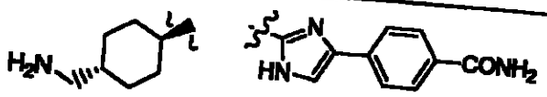
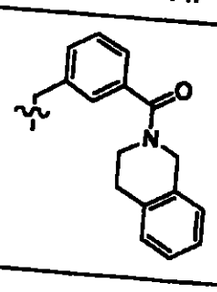
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
177				490.0
178				465.0
179				450.0
180				508.0
181				449.0
183				471.1
187				489.0
188				518.2

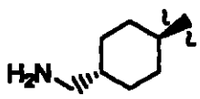
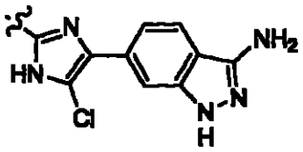
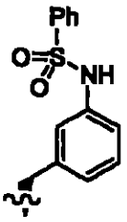
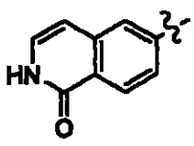
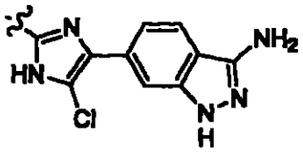
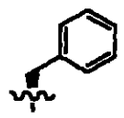
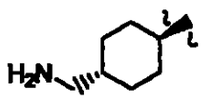
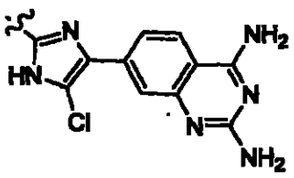
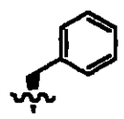
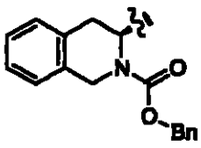
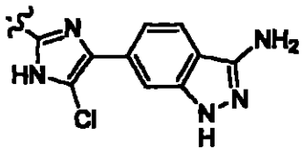
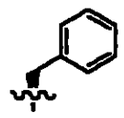
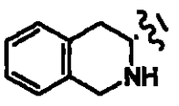
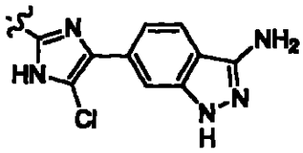
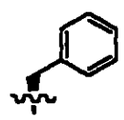
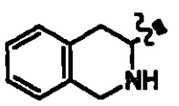
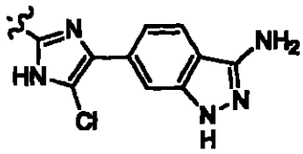
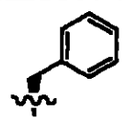
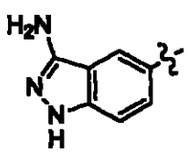
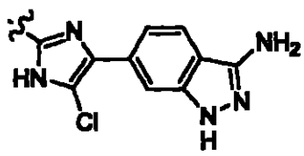
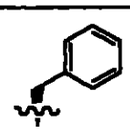
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
189				530.0
190				527.2
191				539.2
192				537.0
194				531.06
195				557.32
196				579.33

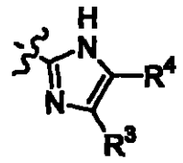
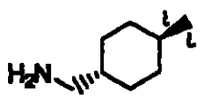
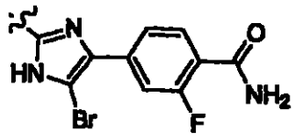
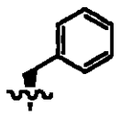
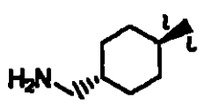
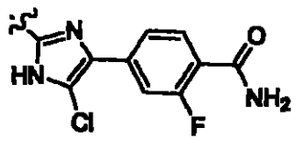
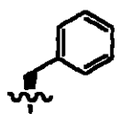
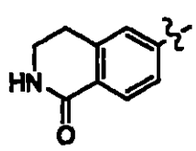
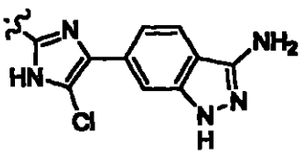
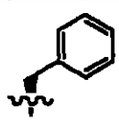
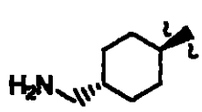
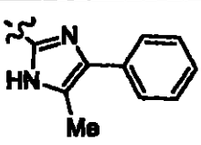
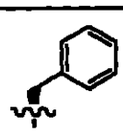
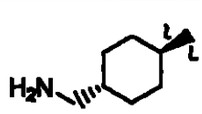
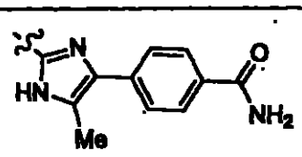
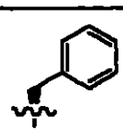
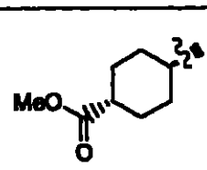
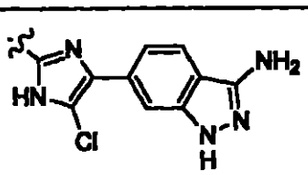
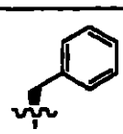
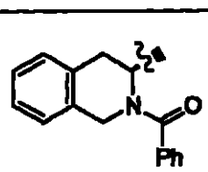
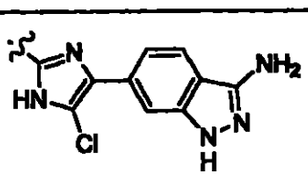
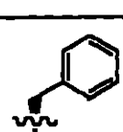
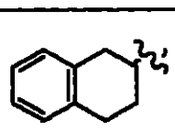
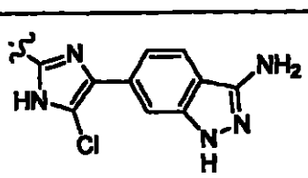
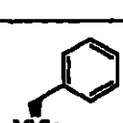
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
197				579.31
198				579.35
199				510.3
203				453.0
213				471.03
214				530.17
215				530.17
217				545.3

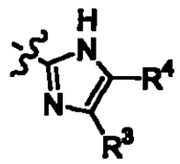
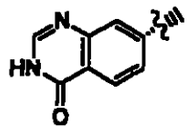
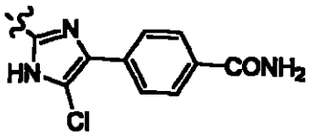
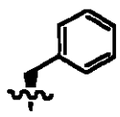
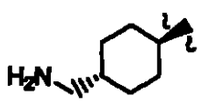
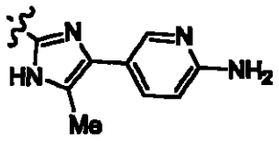
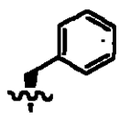
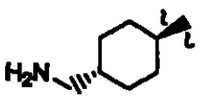
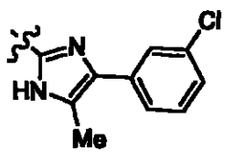
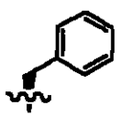
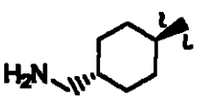
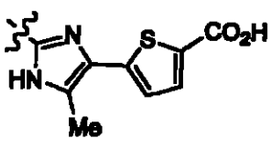
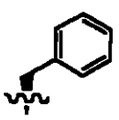
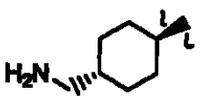
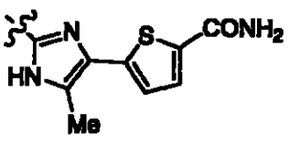
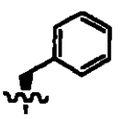
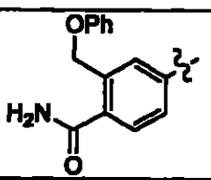
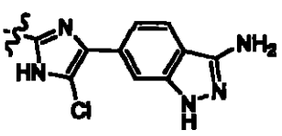
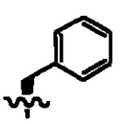
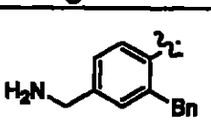
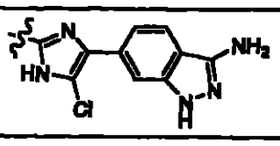
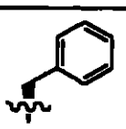
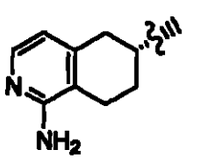
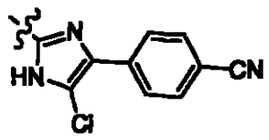
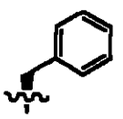
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
218				559.32
219				545.4
220				613.3
221				609.32
222				593.35
223				627.25

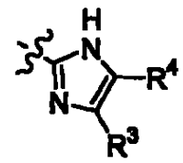
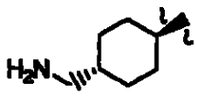
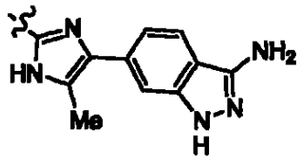
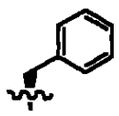
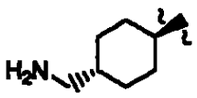
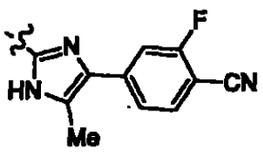
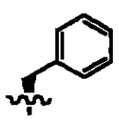
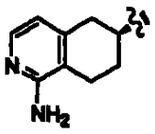
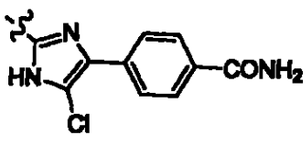
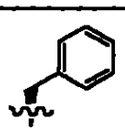
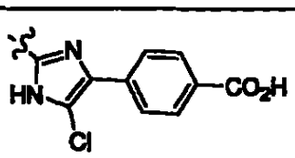
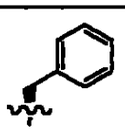
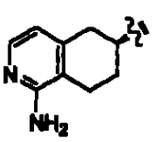
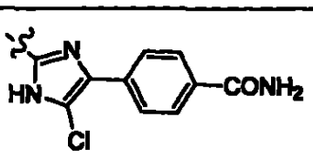
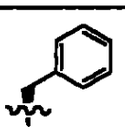
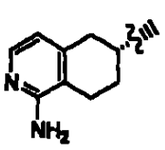
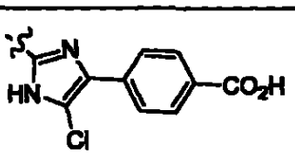
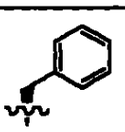
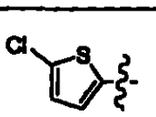
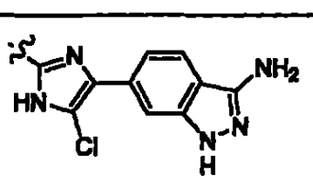
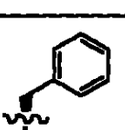
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
224				623.38
225				607.39
226				593.33
227				607.38
228				579.3

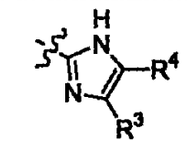
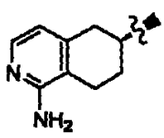
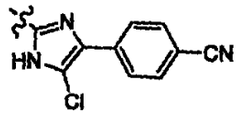
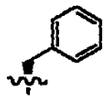
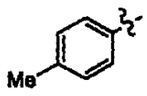
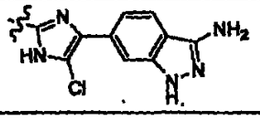
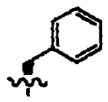
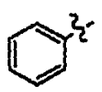
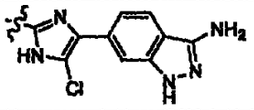
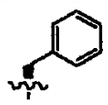
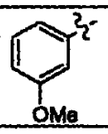
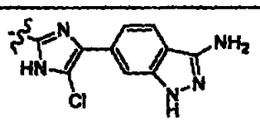
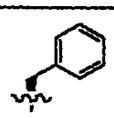
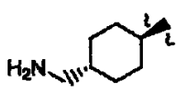
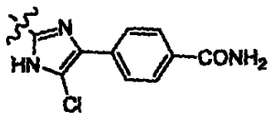
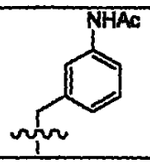
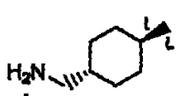
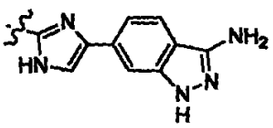
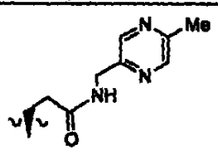
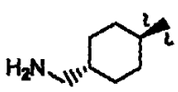
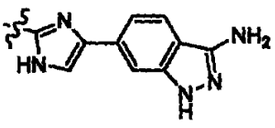
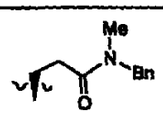
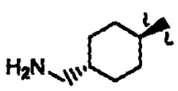
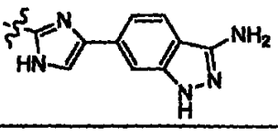
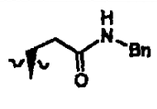
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
229				579.36
230				583.31
231				615.36
232				633.45
233				605.38

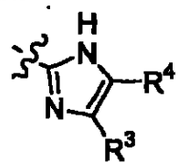
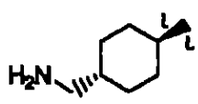
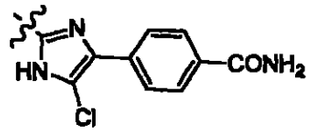
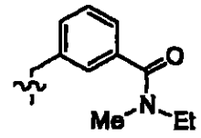
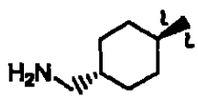
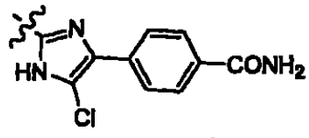
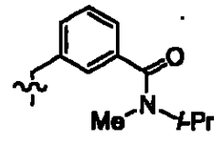
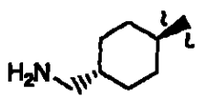
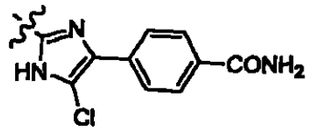
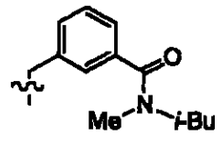
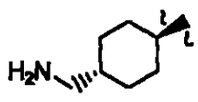
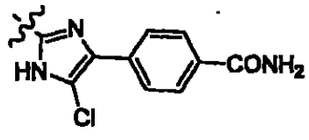
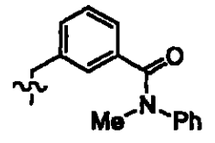
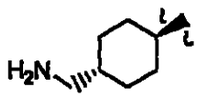
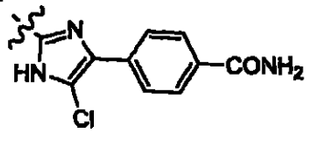
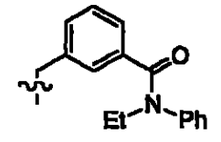
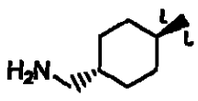
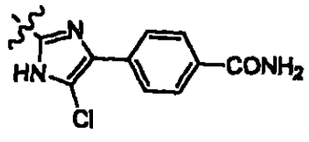
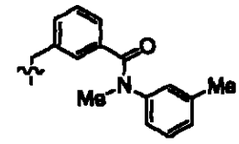
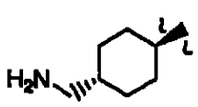
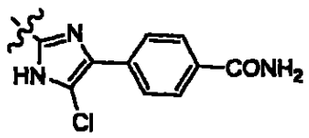
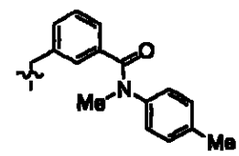
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
235				648.8
238				524.1
239				519.19
241				646.36
242				512.20
243				512.20
244				512.01

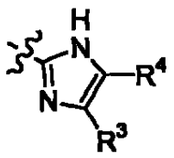
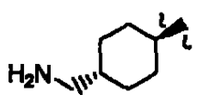
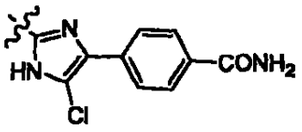
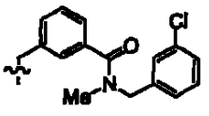
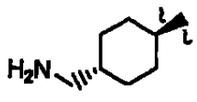
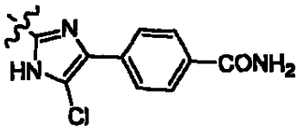
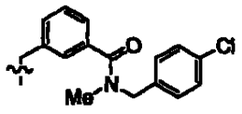
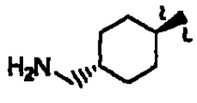
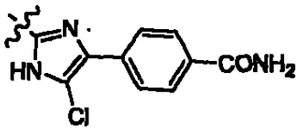
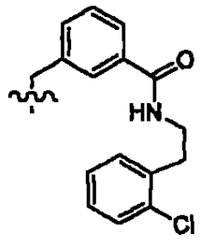
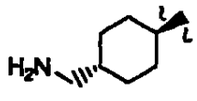
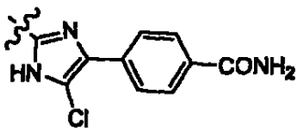
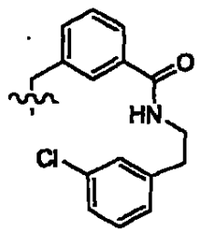
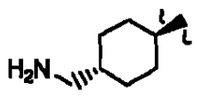
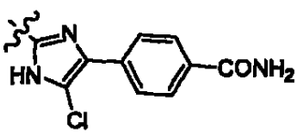
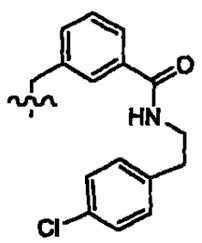
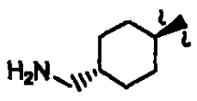
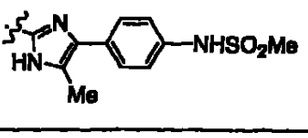
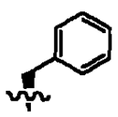
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
248				542.2
249				498.3
250				526.2
251				417.4
252				460.3
253				521.2
254				616.2
255				511.2

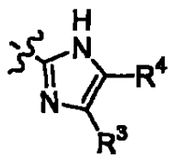
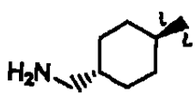
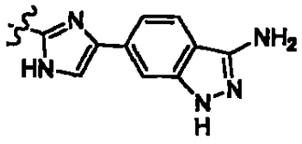
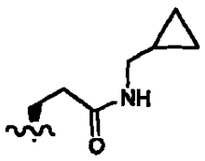
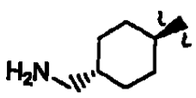
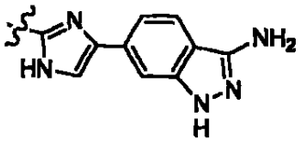
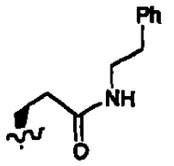
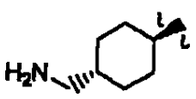
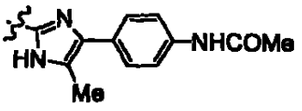
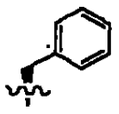
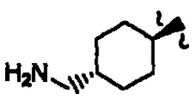
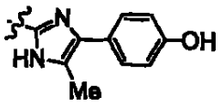
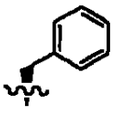
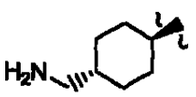
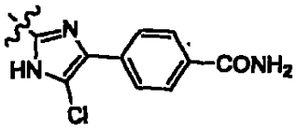
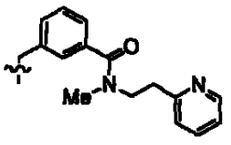
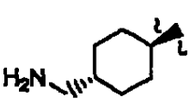
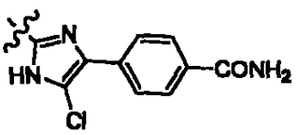
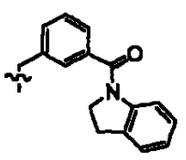
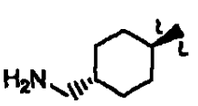
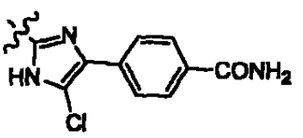
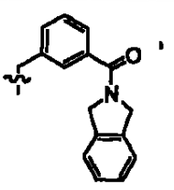
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
266				525.2
267				433.3
268				451.3
269				467.2
270				466.3
271				606.1
272				579.2
273				497.2

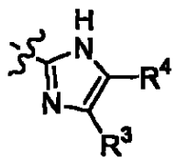
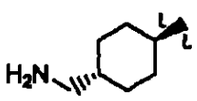
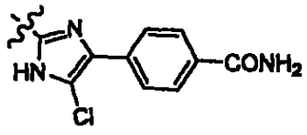
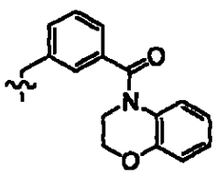
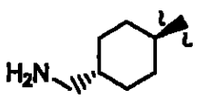
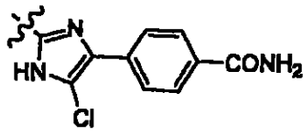
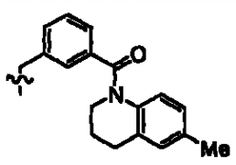
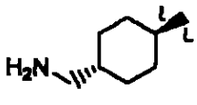
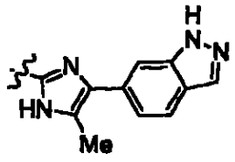
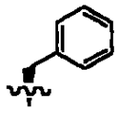
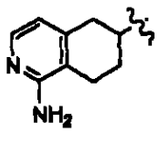
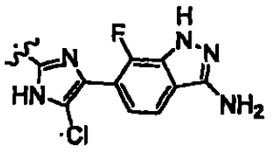
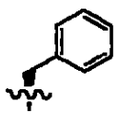
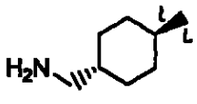
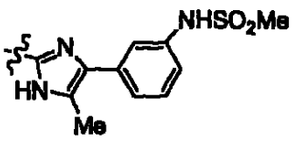
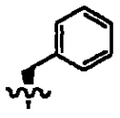
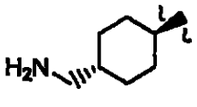
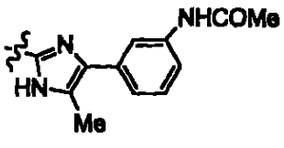
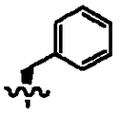
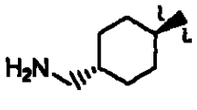
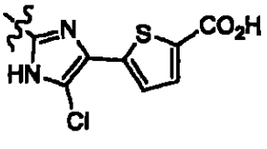
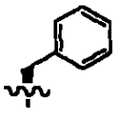
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
256				472.4
257				460.4
261				516.2
262				516.2
263				515.2
264				515.3
265				497.1

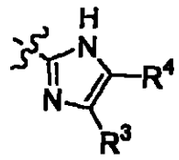
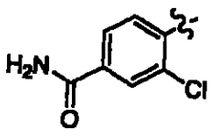
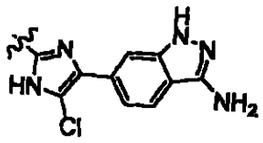
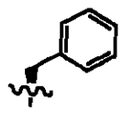
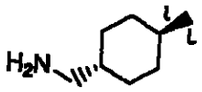
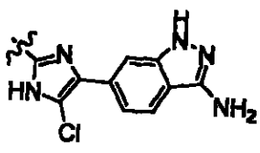
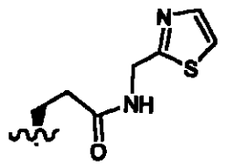
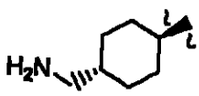
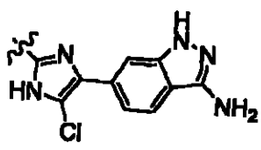
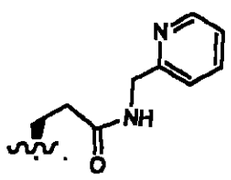
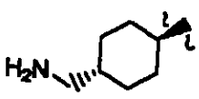
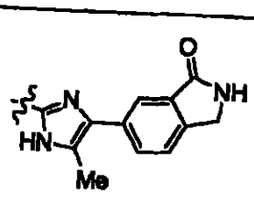
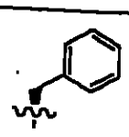
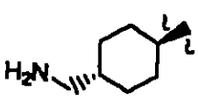
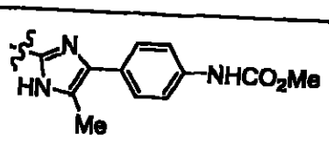
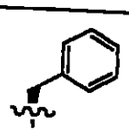
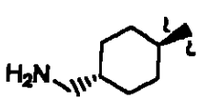
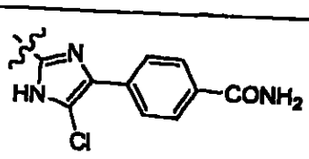
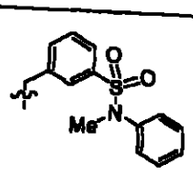
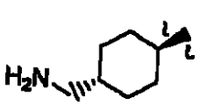
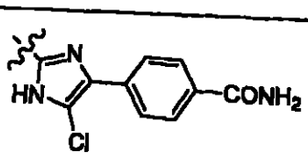
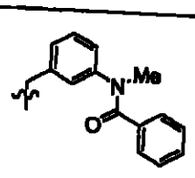
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
274				497.2
275				471.3
276				457.3
277				487.3
278				537.2
279				545.3
280				543.3
281				529.3

Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
282				565.4
283				579.4
284				593.4
285				613.4
286				627.4
287				627.4
288				627.4

Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
289				661.4
290				661.4
291				661.4
292				661.4
293				661.4
294				510.3

Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
295				493.4
296				543.4
297				474.3
298				433.3
299				642.5
300				625.4
301				625.4

Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
302				641.4
303				653.5
304				457.3
305				545.3
306				510.3
307				474.4
308				487.2

Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
309				534.3
310				558.3
311				552.3
312				472.3
313				490.3
314				649.2
315				613.3

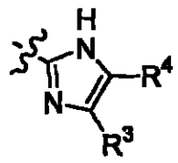
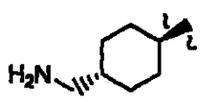
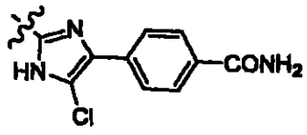
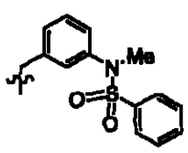
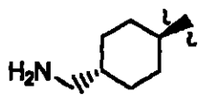
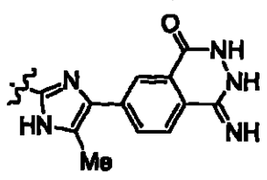
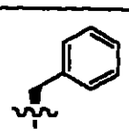
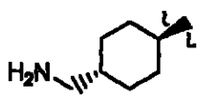
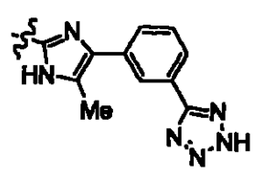
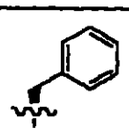
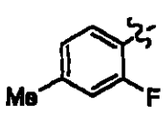
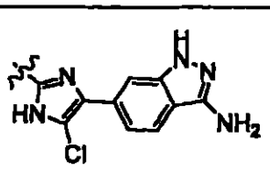
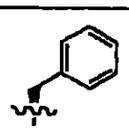
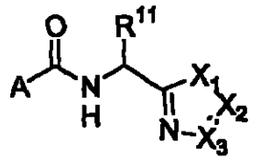
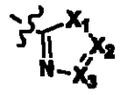
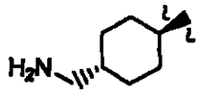
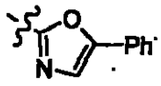
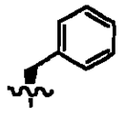
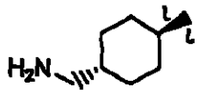
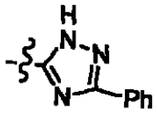
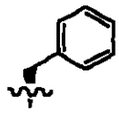
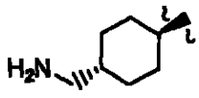
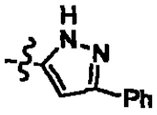
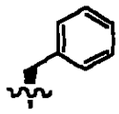
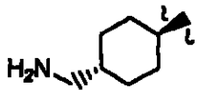
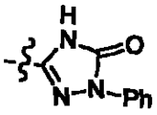
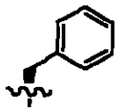
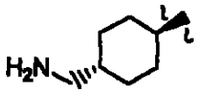
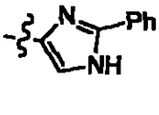
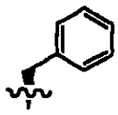
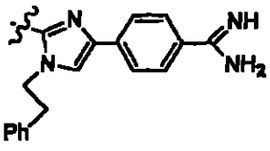
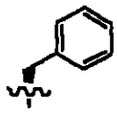
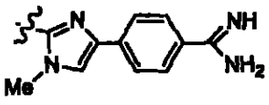
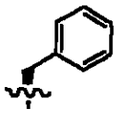
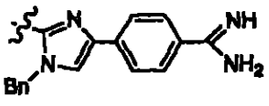
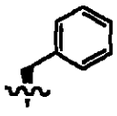
Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
316				649.2
317				500.3
318				485.3
319				489.3

Table 2



Ex #	A		R^{11}	Mass spec (m/z) $(M+H)^+$
48				404.3
49				404.2
50				403.1
51				420.1
52				403.3
125				514.3
126				424.2
127				500.2

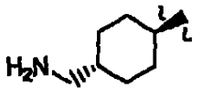
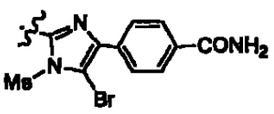
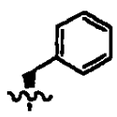
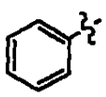
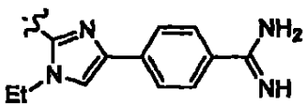
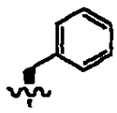
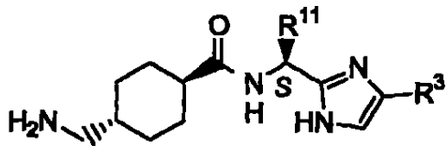
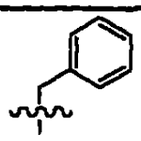
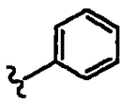
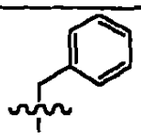
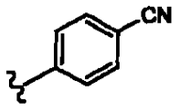
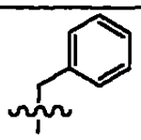
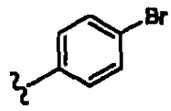
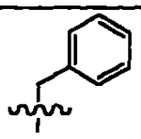
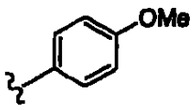
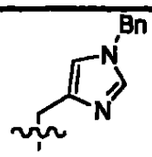
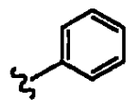
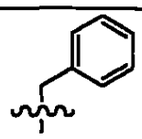
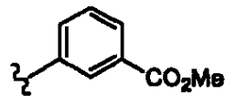
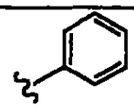
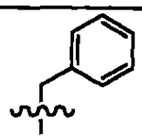
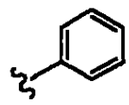
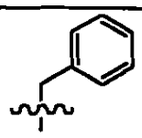
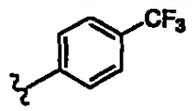
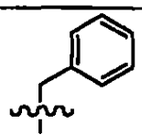
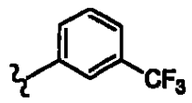
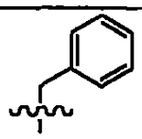
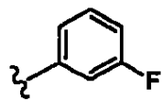
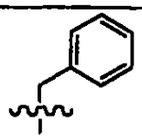
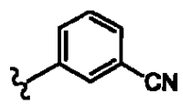
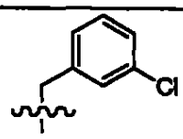
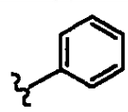
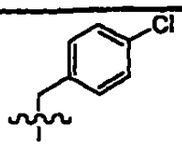
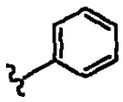
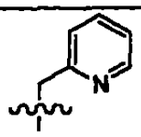
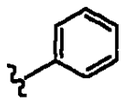
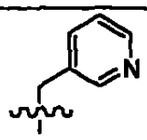
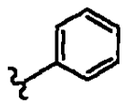
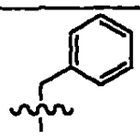
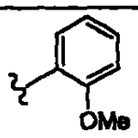
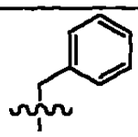
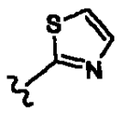
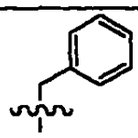
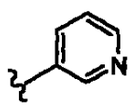
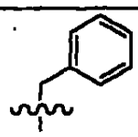
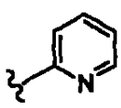
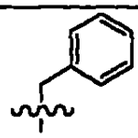
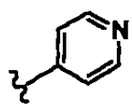
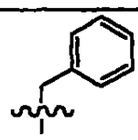
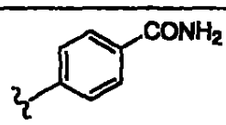
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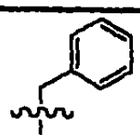
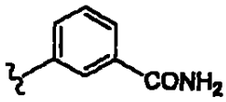
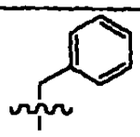
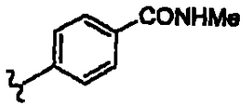
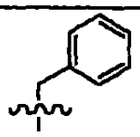
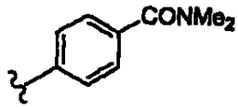
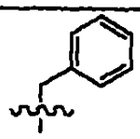
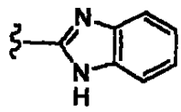
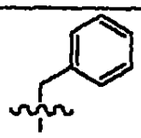
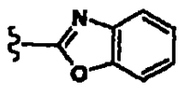
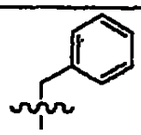
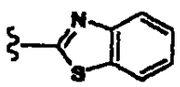
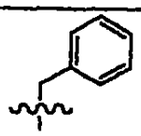
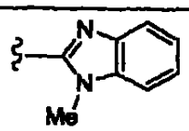
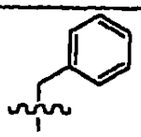
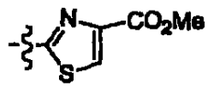
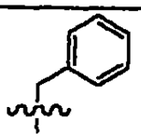
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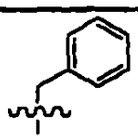
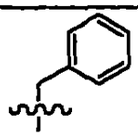
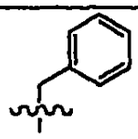
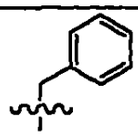
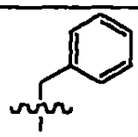
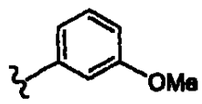
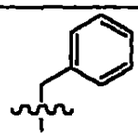
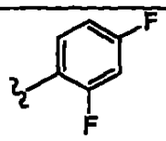
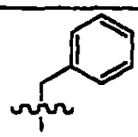
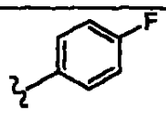
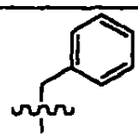
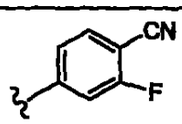
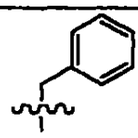
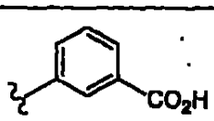


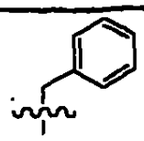
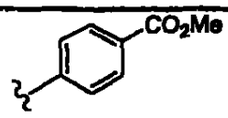
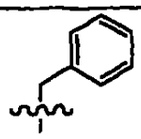
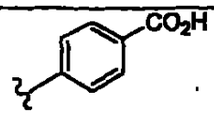
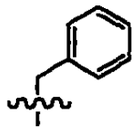
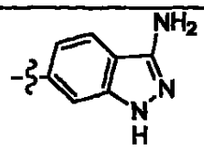
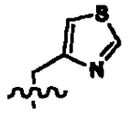
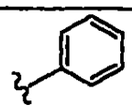
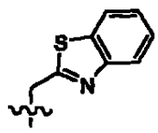
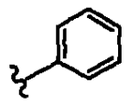
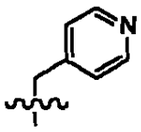
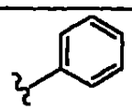
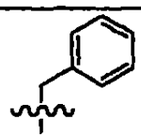
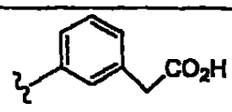
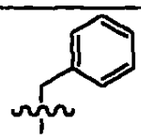
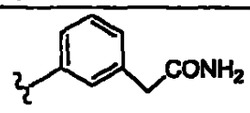
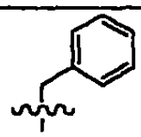
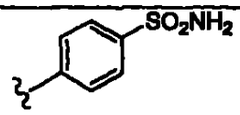
Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
2			403.2
3			428.15
4			481.09
5			433.25

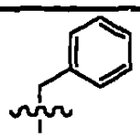
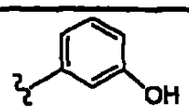
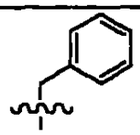
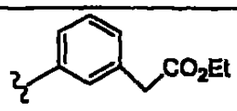
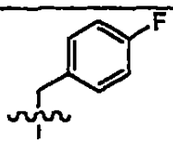
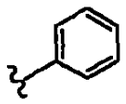
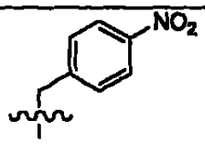
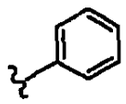
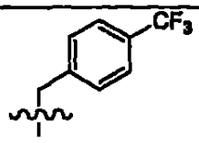
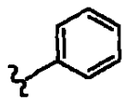
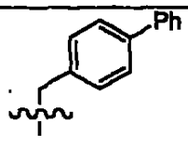
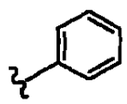
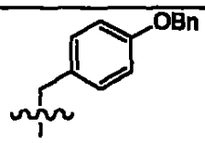
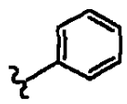
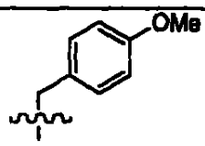
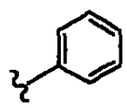
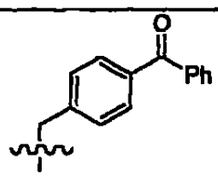
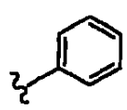
Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
6			483.23
7			461.25
8	Me		327.21
9			417.27
10			471.24
11			471.24
12			421.24
13			428.30
16			437.21

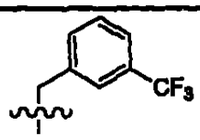
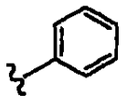
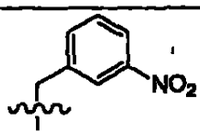
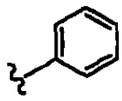
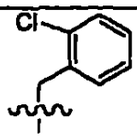
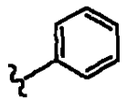
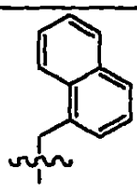
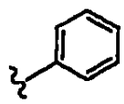
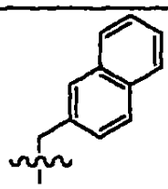
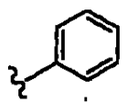
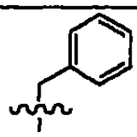
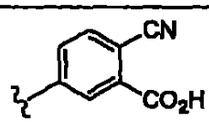
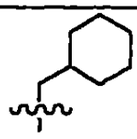
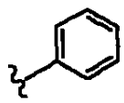
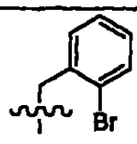
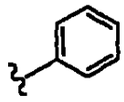
Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
17			437.21
18			404.25
19			404.25
20			433.26
21			432.18
22			404.25
23			404.25
24			404.25
28			446.26

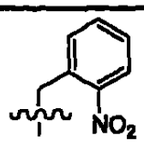
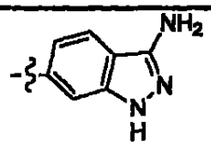
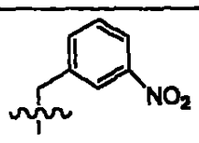
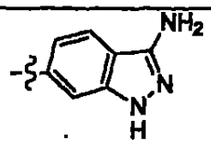
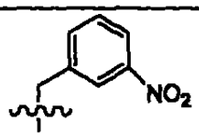
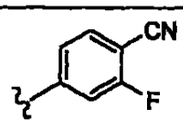
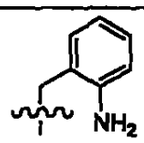
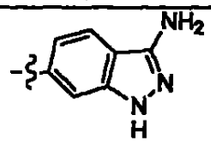
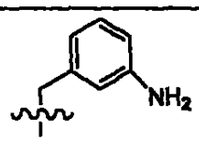
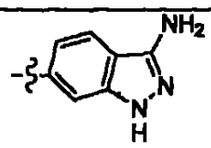
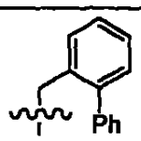
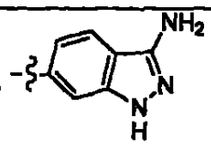
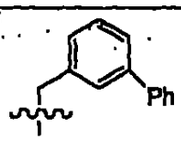
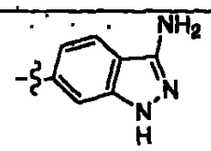
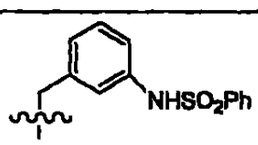
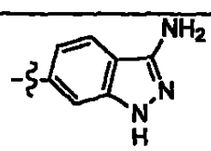
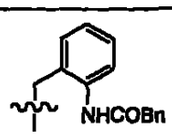
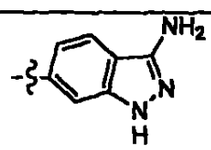
Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
29			446.2
30			460.27
31			474.29
32			443.25
33			444.24
34			460.22
35			457.27
36			468.21
37		$-CO_2Me$	385.33

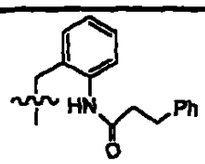
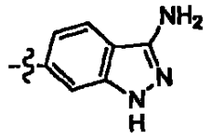
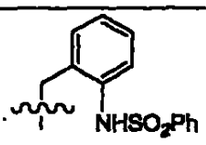
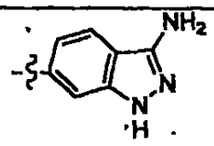
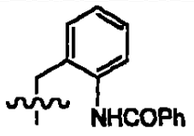
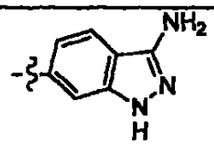
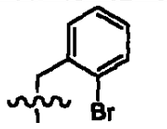
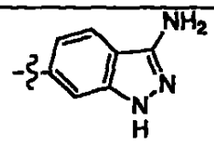
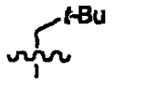
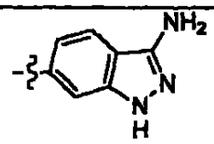
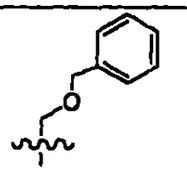
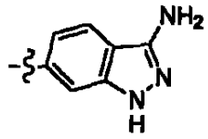
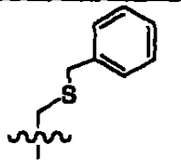
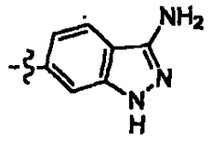
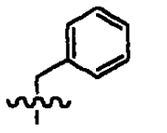
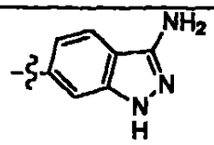
Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
38		$-CO_2H$	371.21
39		$-CONHCH_2CO_2Et$	478.24
40		$-CONHCH_2CO_2H$	428.22
41		-CONHBn	460.27
62			433.22
63			439.23
64			421.24
65			446.23
66			447.24

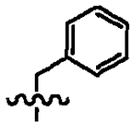
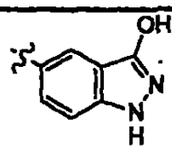
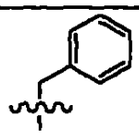
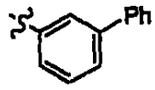
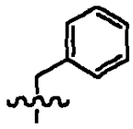
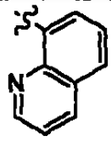
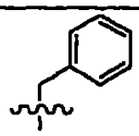
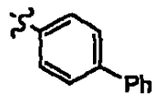
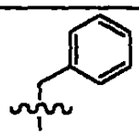
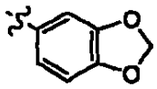
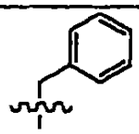
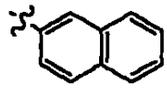
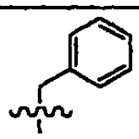
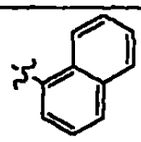
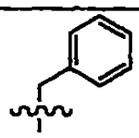
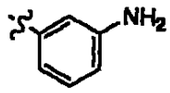
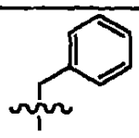
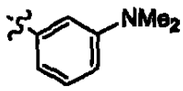
Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
67			461.26
68			447.24
69			458.27
79			410.2
80			460.1
81			404.0
87			461.1
88			460.2
89			482.1

Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
90			419.2
91			489.2
94			421.3
95			448.2
96			471.3
97			479.3
98			509.3
99			433.3
100			507.5

Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
101			471.4
102			448.2
103			437.4
104			453.5
105			453.4
109			472.3
110			409.4
111			481.3

Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
148			503.2
149			503.1
150			491.0
151			473.3
152			473.2
153			534.3
154			534.3
156			613.1
159			591.3

Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
163			605.3
164			613.2
166			577.3
167			537.9
168			438.1
169			488.1
170			504.1
201			457.9

Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
202			459.2
207			479.3
208			454.3
209			479.3
210			447.3
211			453.2
212			453.3
216			418.3
234			446.3

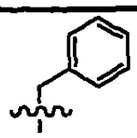
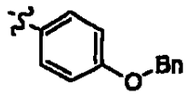
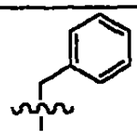
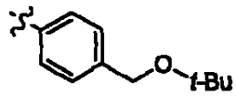
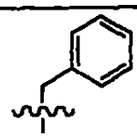
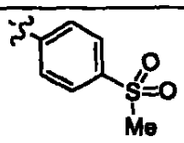
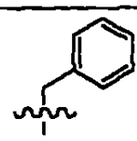
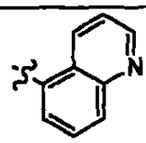
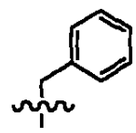
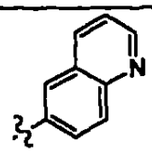
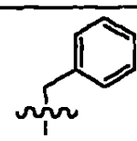
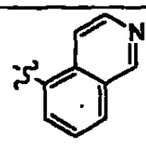
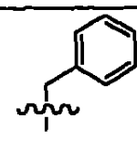
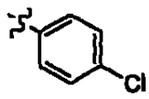
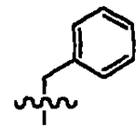
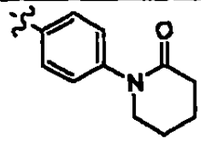
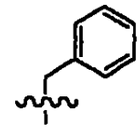
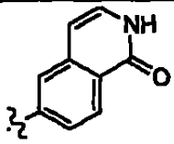
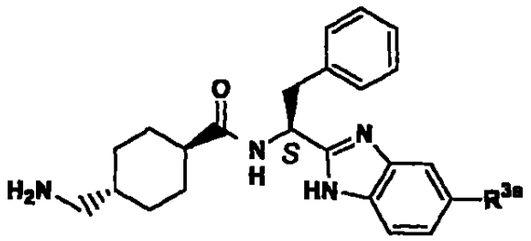
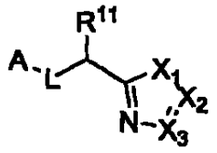
Ex	R^{11}	R^3	Mass spec (m/z), $(M+H)^+$
236			509.3
237			489.3
240			481.2
245			454.3
246			454.3
247			454.3
258			437.3
259			500.3
260			470.3

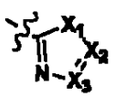
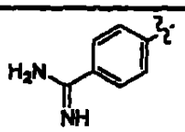
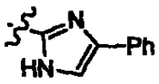
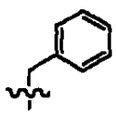
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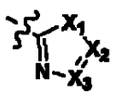
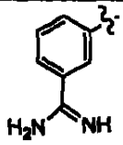
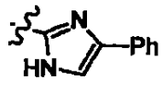
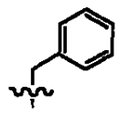
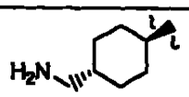
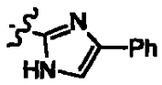
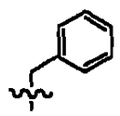
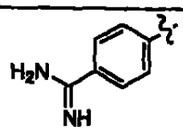
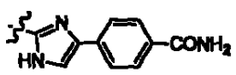
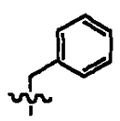
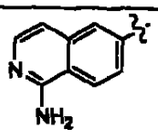
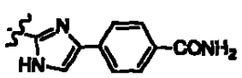
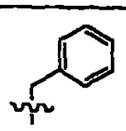
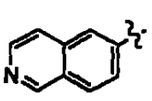
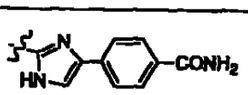
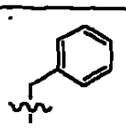
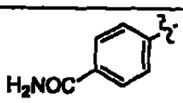
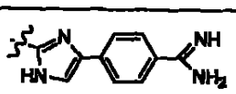
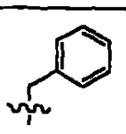
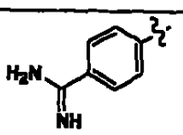
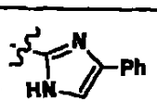
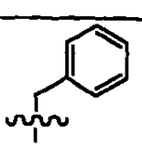
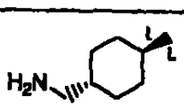
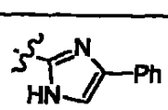
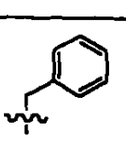


Ex #	R^{3a}	Mass spec (m/z) $(M+H)^+$
42	CO_2Et	435.3
43	CO_2H	421.2
44	$CONH_2$	420.2
45	$-CH_2CO_2Et$	463.4
46	$-CH_2CO_2H$	435.4
47	$-CH_2CONH_2$	434.3

Table 5



Ex #	A	L		R^{11}	Mass spec (m/z) $(M+H)^+$
53		-NHCO-			410.20

Ex #	A	L		R^{11}	Mass spec (m/z) $(M+H)^+$
54		-NHCO-			410.20
55		-NHCO-			410.20
56		-NHCO-			453.20
57		-NHCO-			477.3
58		-NHCO-			462.19
59		-NHCO-			453.4
61		-NHCOCH$_2$-			424.21
77		NHCONH			418.1

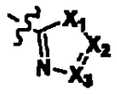
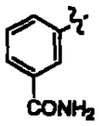
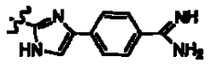
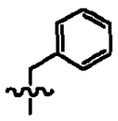
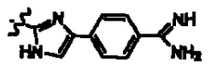
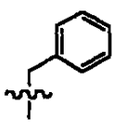
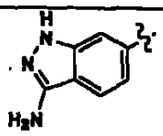
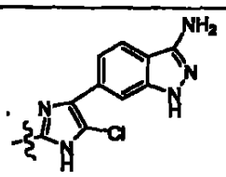
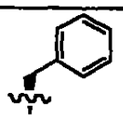
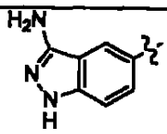
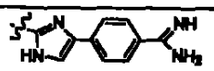
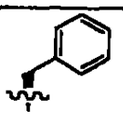
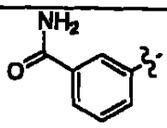
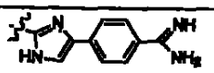
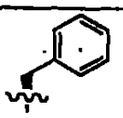
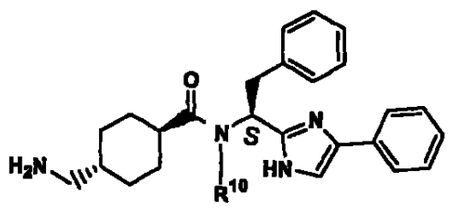
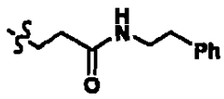
Ex #	A	L		R^{11}	Mass spec (m/z) $(M+H)^+$
92		-NHCO-			453.2
93		-NHCO-			410.2
138		$-CH_2CONH-$			526.3
184		$-SO_2NH-$			501.5
185		$-SO_2NH-$			489.0

Table 6

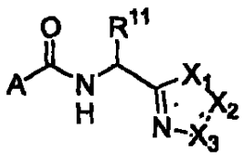


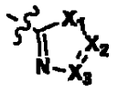
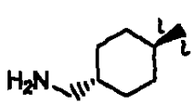
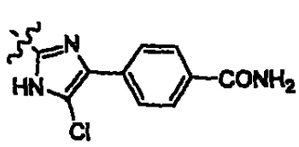
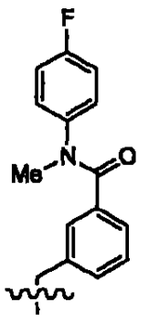
Ex #	R^{10}	Mass spec (m/z) $(M+H)^+$
70	Bn	493.20

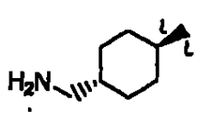
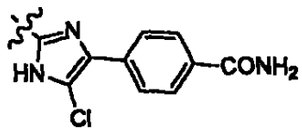
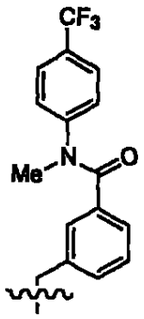
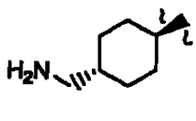
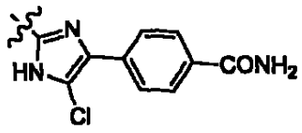
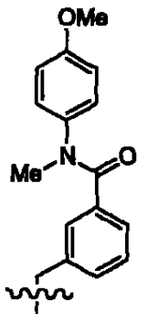
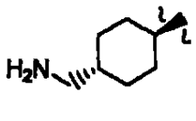
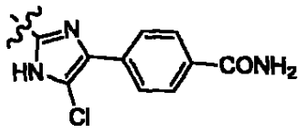
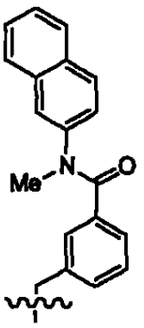
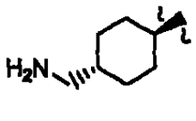
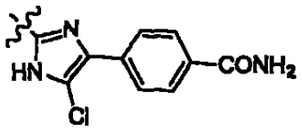
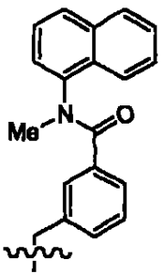
Ex #	R^{10}	Mass spec (m/z) $(M+H)^+$
71	$-CH_2CH_2Ph$	507.31
72	$-CH_2CH_2CO_2Et$	489.62
74	$-CH_2CH_2CONH_2$	474.62
85		578.4

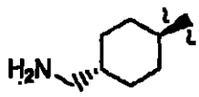
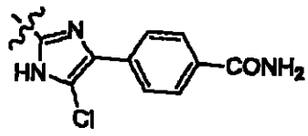
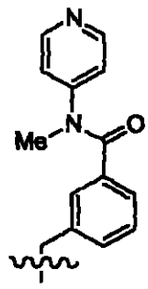
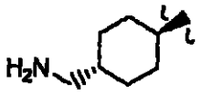
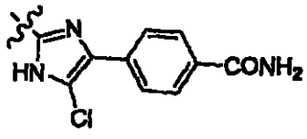
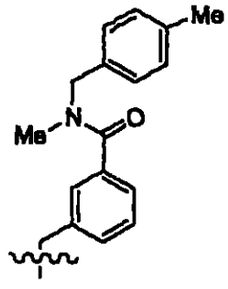
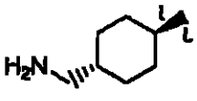
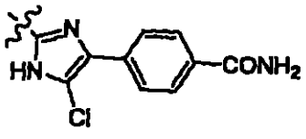
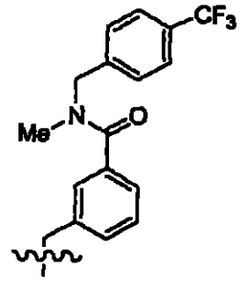
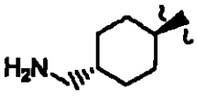
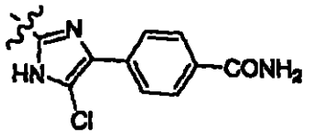
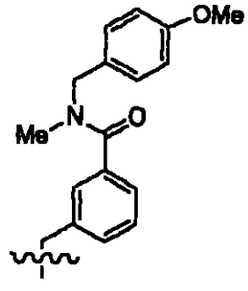
[00742] Using combinations of the above described synthetic routes and experimental procedures along with methods known to one skilled in the art of organic synthesis, additional compounds of this invention as shown below in Table 6 can be prepared.

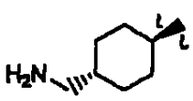
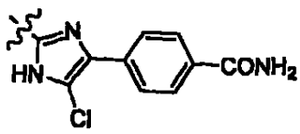
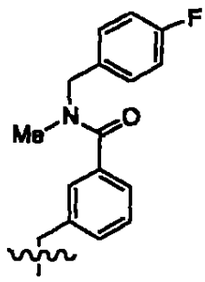
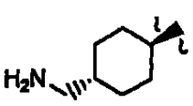
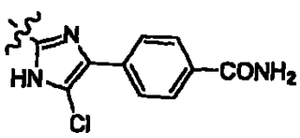
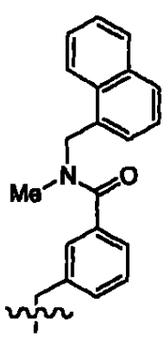
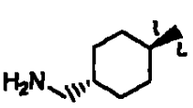
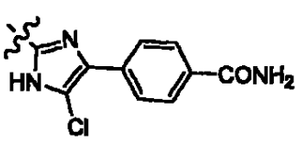
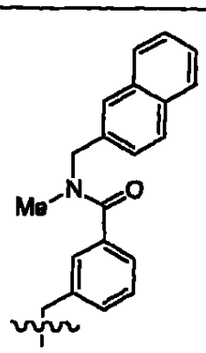
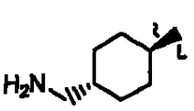
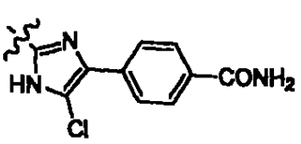
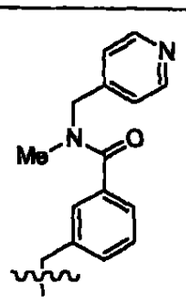
Table 7

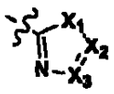
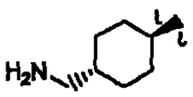
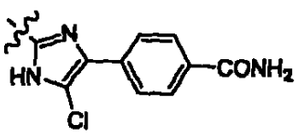
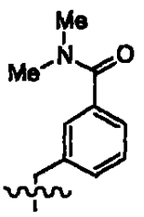
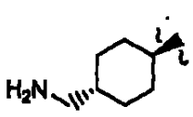
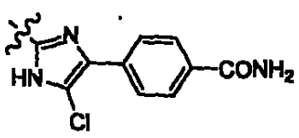
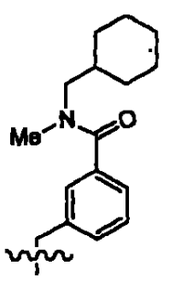
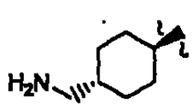
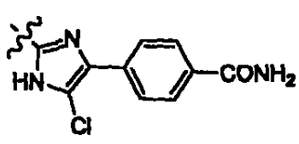
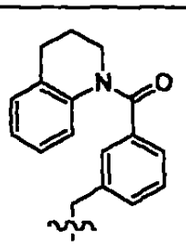
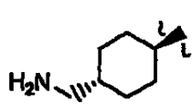
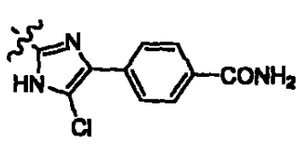
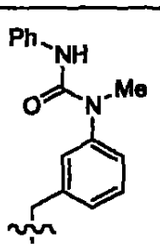
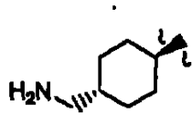
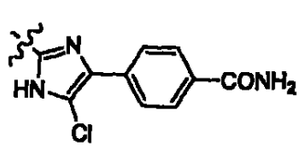
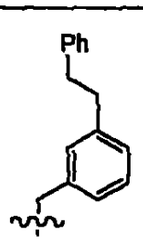


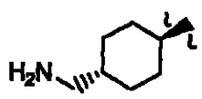
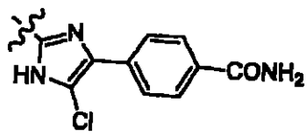
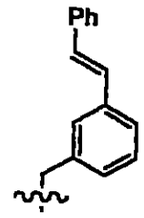
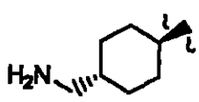
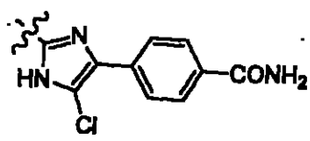
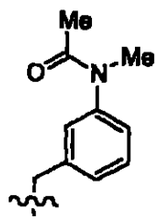
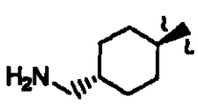
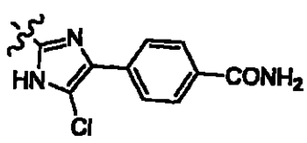
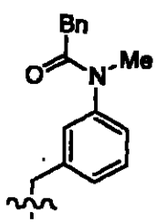
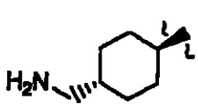
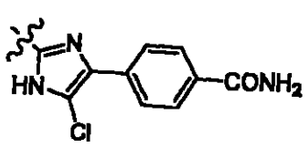
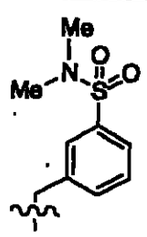
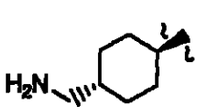
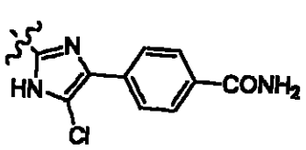
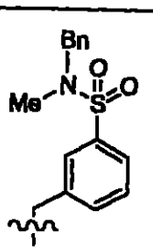
Ex #	A		R^{11}
1001			

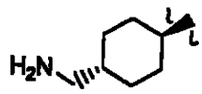
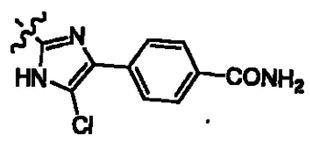
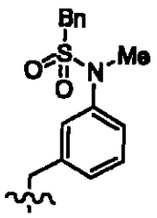
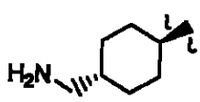
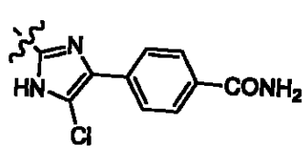
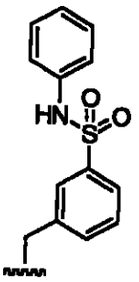
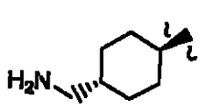
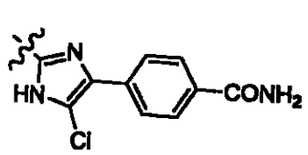
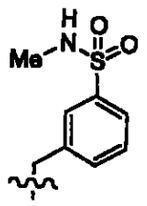
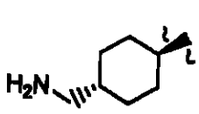
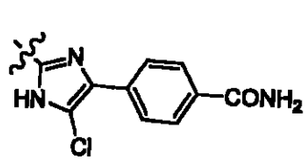
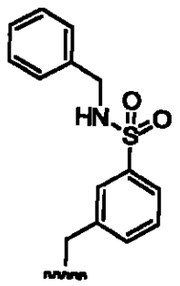
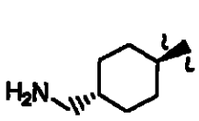
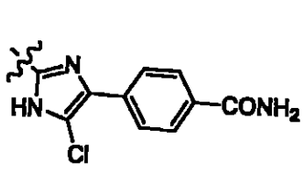
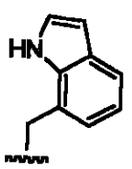
Ex #	A		R^{11}
1002			
1003			
1004			
1005			

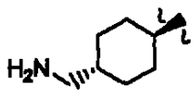
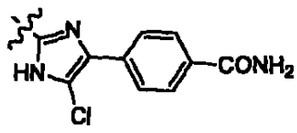
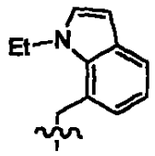
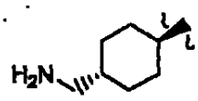
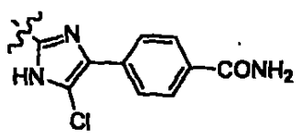
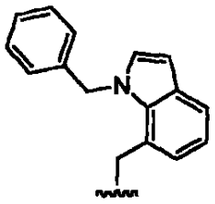
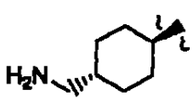
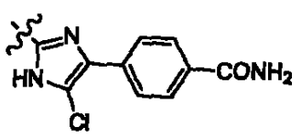
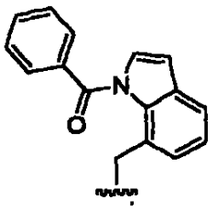
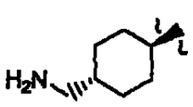
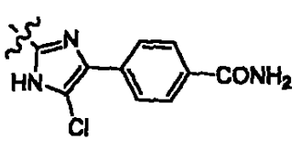
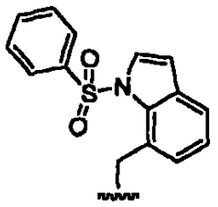
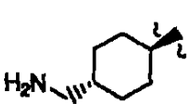
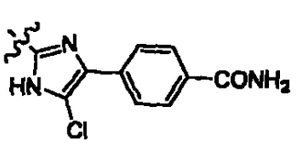
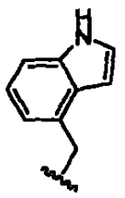
Ex #	A		R^{11}
1006			
1007			
1008			
1009			

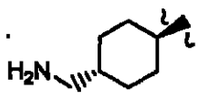
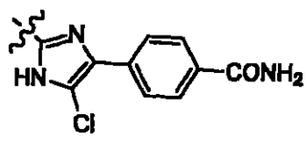
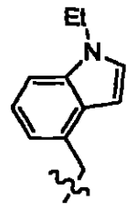
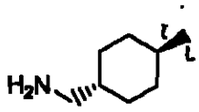
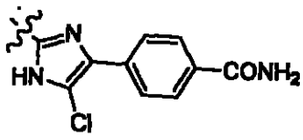
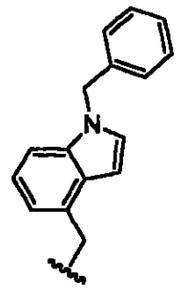
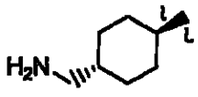
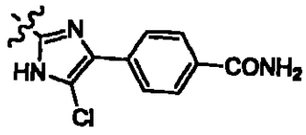
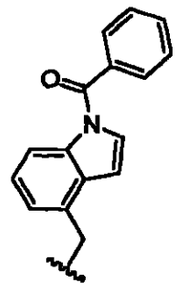
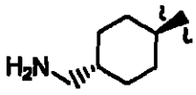
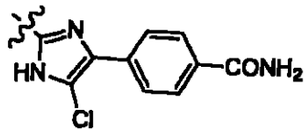
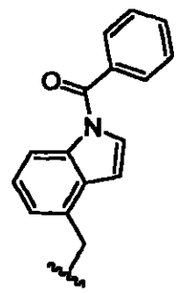
Ex #	A		R^{11}
1010			
1011			
1012			
1013			

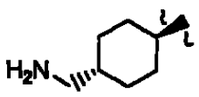
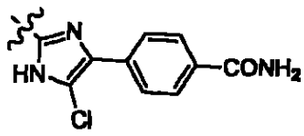
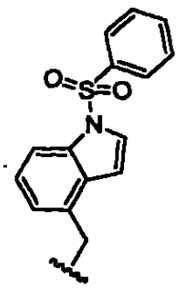
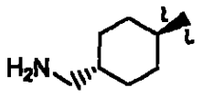
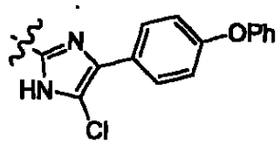
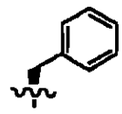
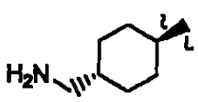
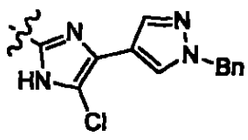
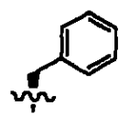
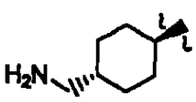
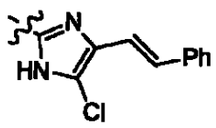
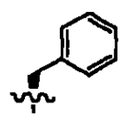
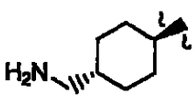
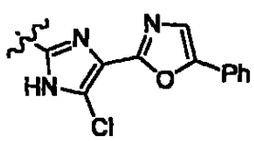
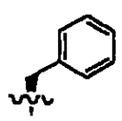
Ex #	A		R^{11}
1014			
1016			
1017			
1018			
1019			

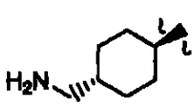
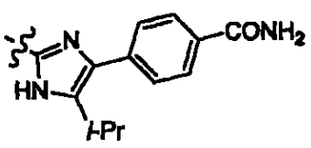
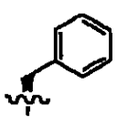
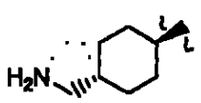
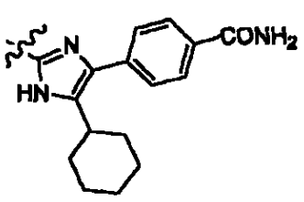
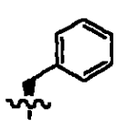
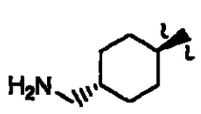
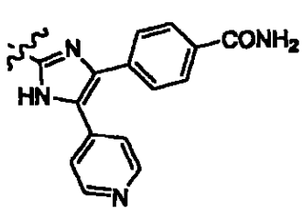
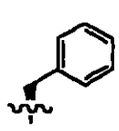
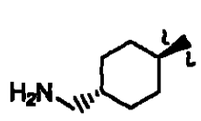
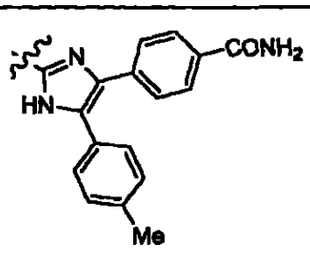
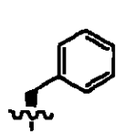
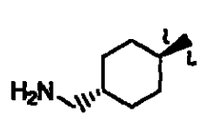
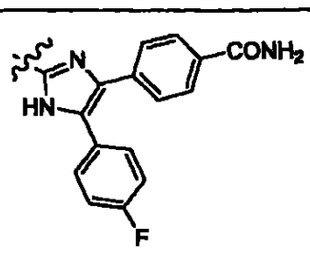
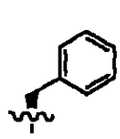
Ex #	A		R^{11}
1020			
1021			
1022			
1024			
1025			

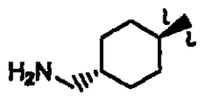
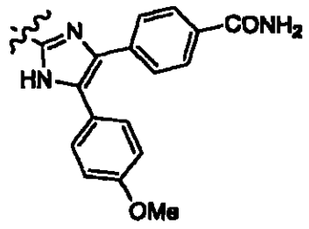
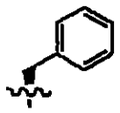
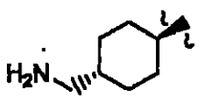
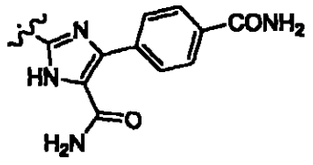
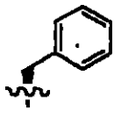
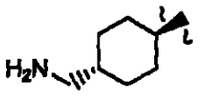
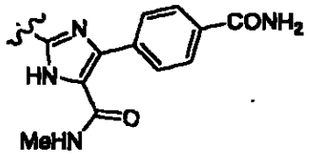
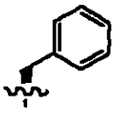
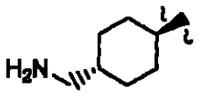
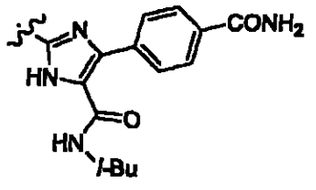
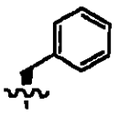
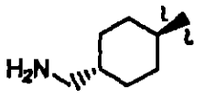
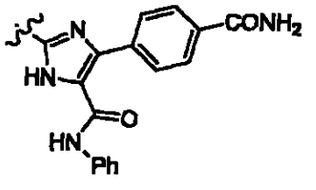
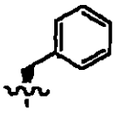
Ex #	A		R^{11}
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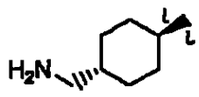
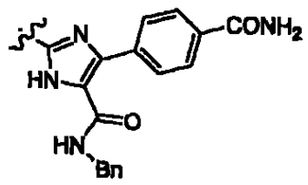
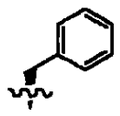
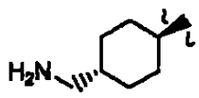
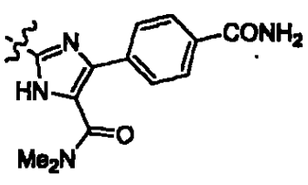
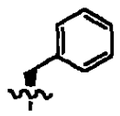
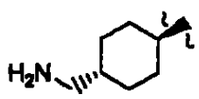
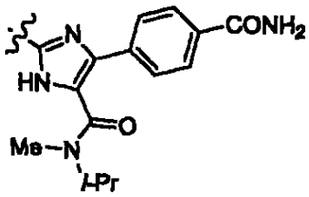
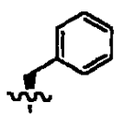
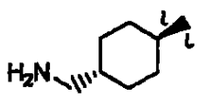
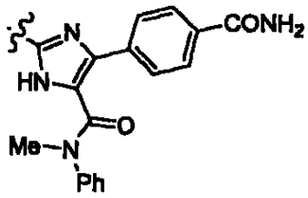
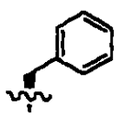
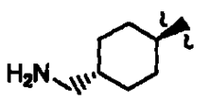
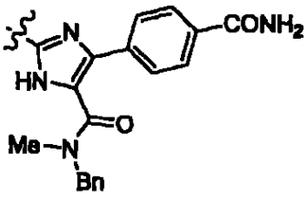
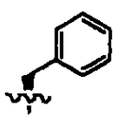
Ex #	A		R^{11}
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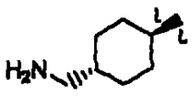
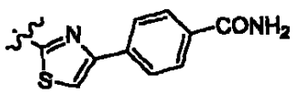
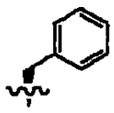
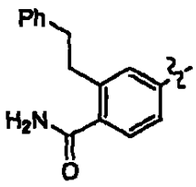
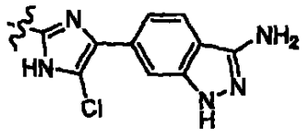
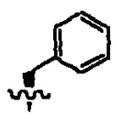
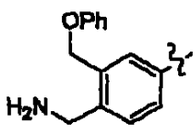
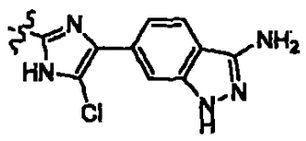
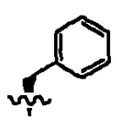
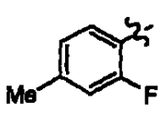
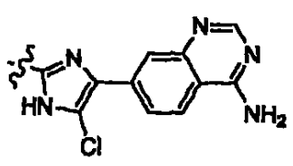
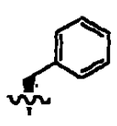
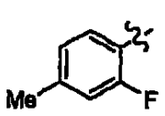
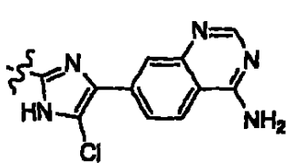
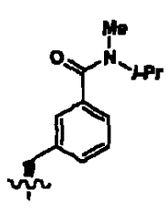
Ex #	A		R^{11}
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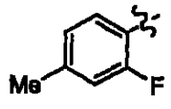
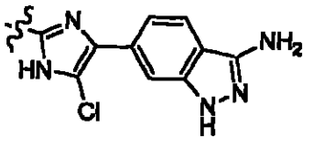
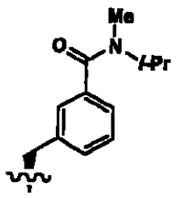
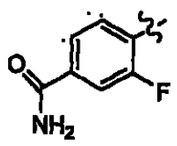
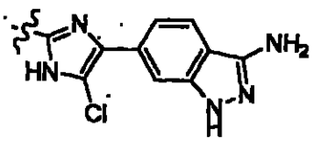
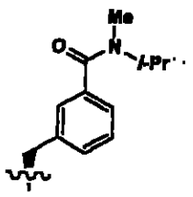
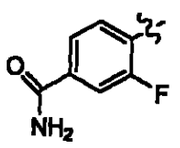
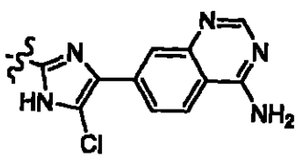
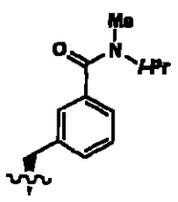
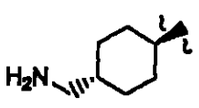
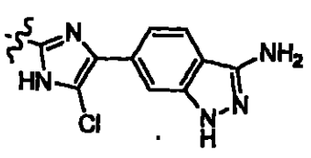
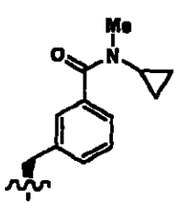
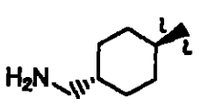
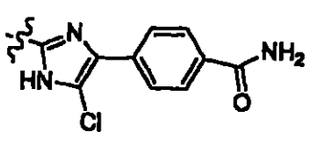
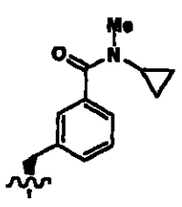
Ex #	A		R^{11}
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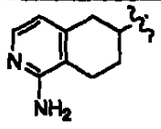
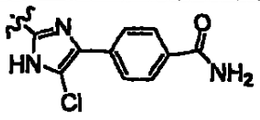
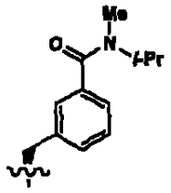
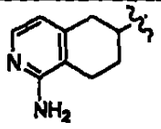
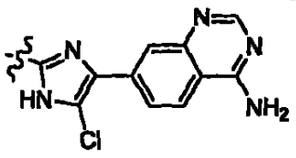
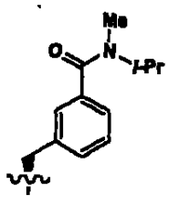
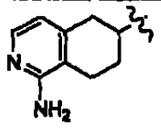
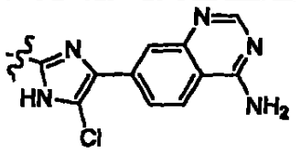
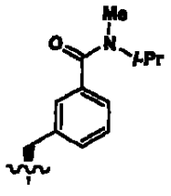
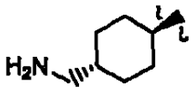
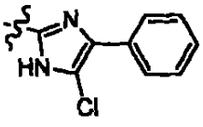
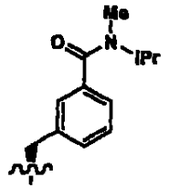
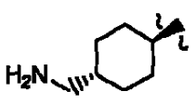
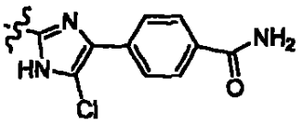
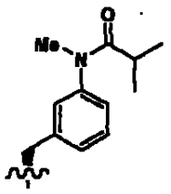
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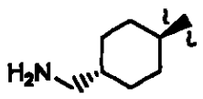
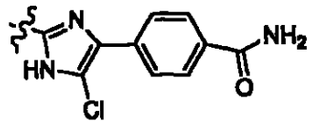
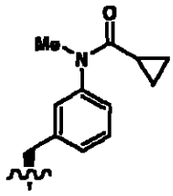
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Ex #	A		R^{11}
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Ex #	A		R^{11}
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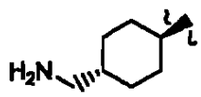
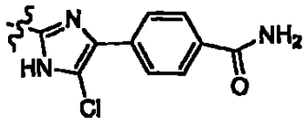
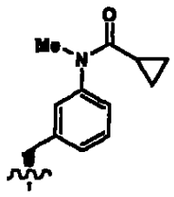
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Ex #	A		R^{11}
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Ex #	A		R11
1077			

UTILITY

[00743] The compounds of this invention are inhibitors of factor XIa and are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals (i.e., factor XIa-associated disorders). In general, a thromboembolic disorder is a circulatory disease caused by blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). The term "thromboembolic disorders" as used herein includes arterial cardiovascular thromboembolic disorders, venous cardiovascular or cerebovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart. The term "thromboembolic disorders" as used herein also includes specific disorders selected from, but not limited to, unstable angina or other acute coronary syndromes, atrial fibrillation, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism

Ex #	A		R^{11}
1077			

UTILITY

[00743] The compounds of this invention are inhibitors of factor XIa and are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals (i.e., factor XIa-associated disorders). In general, a thromboembolic disorder is a circulatory disease caused by blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). The term "thromboembolic disorders" as used herein includes arterial cardiovascular thromboembolic disorders, venous cardiovascular or cerebovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart. The term "thromboembolic disorders" as used herein also includes specific disorders selected from, but not limited to, unstable angina or other acute coronary syndromes, atrial fibrillation, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis. It is noted that thrombosis includes occlusion (*e.g.*, after a bypass) and reocclusion (*e.g.*, during or after percutaneous *trans*luminal coronary angioplasty). The thromboembolic disorders may result from conditions including but not limited to atherosclerosis, surgery or surgical complications, prolonged

immobilization, arterial fibrillation, congenital thrombophilia, cancer, diabetes, effects of medications or hormones, and complications of pregnancy. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of serine proteases involved in the coagulation cascade and/or contact activation system, more specifically, inhibition of the coagulation factors: factor XIa, factor VIIa, factor IXa, factor Xa, plasma kallikrein or thrombin.

[00744] The compounds of this invention also are inhibitors of plasma kallikrein and are useful as anti-inflammatory agents for the treatment or prevention of diseases associated with an activation of the contact activation system (i.e., plasma kallikrein associated disorders). In general, a contact activation system disorder is a disease caused by activation of blood on artificial surfaces, including prosthetic valves or other implants, indwelling catheters, stents, cardiopulmonary bypass, hemodialysis, microorganism (e.g., bacteria, virus), or other procedures in which blood is exposed to an artificial surface that promotes contact activation, blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). It also includes systemic inflammatory response syndrome, sepsis, acute respiratory distress syndrome, hereditary angioedema or other inherited or aquired deficencies of contact activation components or their inhibitors (plasma kallikrein, factor XIIa, high molecular weight kininogen, C1-esterase inhibitor). It may also include acute and chronic inflammations of joints, vessels, or other mammalian organs.

[00745] The effectiveness of compounds of the present invention as inhibitors of the coagulation factors XIa, VIIa, IXa, Xa, plasma kallikrein or thrombin, can be determined using a relevant purified serine protease, respectively, and an appropriate synthetic substrate. The rate of hydrolysis of the chromogenic or fluorogenic substrate by the relevant serine protease was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA (para nitroaniline), which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm, or the release of AMC (amino methylcoumarin, which was monitored spectrofluorometrically by measuring the increase in emission at 460 nm with excitation at 380 nm. A decrease in the rate of absorbance or fluorescence change in the presence of inhibitor is indicative of enzyme inhibition. Such methods are known

to one skilled in the art. The results of this assay are expressed as the inhibitory constant, K_i.

[00746] Factor XIa determinations were made in 50 mM HEPES buffer at pH 7.4 containing 145 mM NaCl, 5 mM KCl, and 0.1% PEG 8000 (polyethylene glycol; JT Baker or Fisher Scientific). Determinations were made using purified human Factor XIa at a final concentration of 75-200 pM (Haematologic Technologies) and the synthetic substrate S-2366 (pyroGlu-Pro-Arg-pNA; Chromogenix) at a concentration of 0.0002-0.00025 M. In general, preferred compounds of the present invention, such as the particular compounds disclosed in the above examples, have been identified to be active and exhibit K_i's of equal to or less than 15 μM in the Factor XIa assay, thereby demonstrating the utility of the compounds of the present invention as especially effective inhibitors of coagulation Factor XIa. More preferred compounds have K_i's of equal to or less than 5 μM, preferably equal to or less than 1 μM, more preferably equal to or less than 0.5 μM.

[00747] Factor VIIa determinations were made in 0.005 M calcium chloride, 0.15 M sodium chloride, 0.05 M HEPES buffer containing 0.5% PEG 8000 at a pH of 7.4. Determinations were made using purified human Factor VIIa (Haematologic Technologies) or recombinant human Factor VIIa (Novo Nordisk) at a final assay concentration of 2-5 nM, recombinant soluble tissue factor at a concentration of 18-35 nM and the synthetic substrate H-D-Ile-Pro-Arg-pNA (S-2288; Chromogenix or BMPM-2; AnaSpec) at a concentration of 0.001 M. In general, compounds tested in the Factor VIIa assay are considered to be active if they exhibit a K_i of equal to or less than 15 μM.

[00748] Factor IXa determinations were made in 0.005 M calcium chloride, 0.1 M sodium chloride, 0.05 M TRIS base and 0.5% PEG 8000 at a pH of 7.4. Determinations were made using purified human Factor IXa (Haematologic Technologies) at a final assay concentration of 20-100 nM and the synthetic substrate PCIXA2100-B (CenterChem) or Pefafluor IXa 3688 (H-D-Leu-Ph'Gly-Arg-AMC; CenterChem) at a concentration of 0.0004-0.0005 M. In general, compounds tested in the Factor IXa assay are considered to be active if they exhibit a K_i of equal to or less than 15 μM.

[00749] Factor Xa determinations were made in 0.1 M sodium phosphate buffer at a pH of 7.4 containing 0.2 M sodium chloride and 0.5% PEG 8000. Determinations were made using purified human Factor Xa (Haematologic Technologies) at a final assay concentration of 150-1000 pM and the synthetic substrate S-2222 (Bz-Ile-Glu (gamma-OMe, 50%)-Gly-Arg-pNA; Chromogenix) at a concentration of 0.0002-0.0003 M. In general, compounds tested in the Factor Xa assay are considered to be active if they exhibit a K_i of equal to or less than 15 μM.

[00750] Plasma kallikrein determinations were made in 0.1 M sodium phosphate buffer at a pH of 7.4 containing 0.2 M sodium chloride and 0.5% PEG 8000. Determinations were made using purified human kallikrein (Enzyme Research Laboratories) at a final assay concentration of 200 pM and the synthetic substrate S-2302 (H-(D)-Pro-Phe-Arg-pNA; Chromogenix) at a concentration of 0.00008-0.0004 M. The Km value used for calculation of Ki was 0.00005 to 0.00007 M. In general, Compounds tested in the plasma kallikrein assay are considered to be active if they exhibit a K_i of equal to or less than 15 μM.

[00751] Thrombin determinations were made in 0.1 M sodium phosphate buffer at a pH of 7.4 containing 0.2 M sodium chloride and 0.5% PEG 8000. Determinations were made using purified human alpha thrombin (Haematologic Technologies or Enzyme Research Laboratories) at a final assay concentration of 200-250 pM and the synthetic substrate S-2366 (pyroGlu-Pro-Arg-pNA; Chromogenix) at a concentration of 0.0002 M. In general, compounds tested in the thrombin assay are considered to be active if they exhibit a K_i of equal to or less than 15 μM.

[00752] In general, preferred compounds of the present invention have demonstrated K_i values of equal to or less than 15 μM in at least one of the above assays, thereby confirming the utility of the compounds of the present invention as effective inhibitors of the coagulation cascade and/or contact activation system, and useful as anticoagulants for the prevention or treatment of thromboembolic disorders in mammals and/or as anti-inflammatory agents for the prevention or treatment of inflammatory disorders in mammals.

[00753] The Michaelis constant, K_m, for substrate hydrolysis by each protease was determined at 25 °C using the method of Lineweaver and Burk. Values of K_i

were determined by allowing the protease to react with the substrate in the presence of the inhibitor. Reactions were allowed to go for periods of 20-180 minutes (depending on the protease) and the velocities (rate of absorbance or fluorescence change versus time) were measured. The following relationships were used to calculate K_i values:

$(v_o-v_s)/v_s = I/(K_i(1 + S/K_m))$ for a competitive inhibitor with one binding site; or

$v_s/v_o = A + ((B-A)/1 + ((IC_{50}/(I)^n)))$ and

$K_i = IC_{50}/(1 + S/K_m)$ for a competitive inhibitor

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

A is the minimum activity remaining (usually locked at zero);

B is the maximum activity remaining (usually locked at 1.0);

n is the Hill coefficient, a measure of the number and cooperativity of potential inhibitor binding sites;

IC_{50} is the concentration of inhibitor that produces 50% inhibition under the assay conditions;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate; and

K_m is the Michaelis constant for the substrate.

[00754] The effectiveness of compounds of the present invention as inhibitors of the coagulation factors XIa, VIIa, IXa, Xa, or thrombin, can be determined using relevant in vivo thrombosis models, including *In Vivo* Electrically-induced Carotid Artery Thrombosis Models and *In Vivo* Rabbit Arterio-venous Shunt Thrombosis Models.

***In Vivo* Electrically-induced Carotid Artery Thrombosis Model:**

[00755] The antithrombotic effect of compounds of the present invention can be demonstrated in the electrically-induced carotid artery thrombosis (ECAT) model in rabbits. In this model, rabbits are anesthetized with a mixture of ketamine (50

mg/kg i.m.) and xylazine (10 mg/kg i.m.). A femoral vein and a femoral artery are isolated and catheterized. The carotid artery is also isolated such that its blood flow can be measured with a calibrated flow probe that is linked to a flowmeter. A stainless steel bipolar hook electrode is placed on the carotid artery and positioned caudally in relationship to the flow probe as a means of applying electrical stimulus. In order to protect the surrounding tissue, a piece of Parafilm is placed under the electrode.

[00756] Test compounds are considered to be effective as anticoagulants based on their ability to maintain blood flow in the carotid artery following the induction of thrombosis by an electrical stimulus. A test compound or vehicle is given as continuous intravenous infusion *via* the femoral vein, starting 1 hour before electrical stimulation and continuing to the end of the test. Thrombosis is induced by applying a direct electrical current of 4 mA for 3 min to the external arterial surface, using a constant current unit and a d.c. stimulator. The carotid blood flow is monitored and the time to occlusion (decrease of blood flow to zero following induction of thrombosis) in minutes is noted. The change in observed blood flow is calculated as a percentage of the blood flow prior to induction of thrombosis and provides a measure of the effect of a test compound when compared to the case where no compound is administered. This information is used to estimate the ED_{50} value, the dose that increases blood flow to 50% of the control (blood flow prior to induction of thrombosis) and is accomplished by nonlinear least square regression.

***In Vivo* Rabbit Arterio-venous Shunt Thrombosis Model:**

[00757] The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing that contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread

covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID_{50} values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

[00758] The anti-inflammatory effect of these compounds can be demonstrated in an Evans Blue dye extravasation assay using C1-esterase inhibitor deficient mice. In this model, mice are dosed with a compound of the present invention, Evans Blue is injected via the tail vein, and extravasation of the blue dye is determined by spectrophotometric means from tissue extracts.

[00759] The ability of the compounds of the current invention to reduce or prevent the systemic inflammatory response syndrome, for example, as observed during on-pump cardiovascular procedures, can be tested in in vitro perfusion systems, or by on-pump surgical procedures in larger mammals, including dogs and baboons. Read-outs to assess the benefit of the compounds of the present invention include for example reduced platelet loss, reduced platelet / white blood cell complexes, reduced neutrophil elastase levels in plasma, reduced activation of complement factors, and reduced activation and/or consumption of contact activation proteins (plasma kallikrein, factor XII, factor XI, high molecular weight kininogen, C1-esterase inhibitors).

[00760] The utility of the compounds of the current invention to reduce or prevent the morbidity and/or mortality of sepsis can be assessed by injecting a mammalian host with bacteria or viruses or extracts there of and compounds of the present invention.Typical read-outs of the efficacy include changes in the LD50 and blood pressure preservation.

[00761] The compounds of the present invention may also be useful as inhibitors of additional serine proteases, notably human thrombin, human plasma kallikrein and human plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, including blood coagulation, fibrinolysis, blood pressure regulation and inflammation, and wound healing catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity of the aforementioned serine proteases, such as myocardial

infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

[00762] The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, anti-inflammatory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

[00763] The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of the present invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to treat (i.e. prevent, inhibit or ameliorate) the thromboembolic and/or inflammatory disease condition or treat the progression of the disease in a host.

[00764] The compounds of the invention are preferably administered alone to a mammal in a therapeutically effective amount. However, the compounds of the invention can also be administered in combination with an additional therapeutic agent, as define below, to a mammal in a therapeutically effective amount. When administered in a combination, the combination of compounds is preferably, but not necessarily, a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*, 27-55, occurs when the effect (in this case, inhibition of the desired target) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased anticoagulant effect, or some other beneficial effect of the combination compared with the individual components.

[00765] By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be

administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

[00766] Compounds which can be administered in combination with the compounds of the present invention include, but are not limited to, anticoagulants, anti-thrombin agents, anti-platelet agents, fibrinolytics, hypolipidemic agents, antihypertensive agents, and anti-ischemic agents.

[00767] Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin, heparin (either unfractionated heparin or any commercially available low molecular weight heparin, for example LOVENOX™), aprotinin, synthetic pentasaccharide, direct acting thrombin inhibitors including hirudin and argatroban, as well as other factor VIIa, VIIIa, IXa, Xa, XIa, thrombin, TAFI, and fibrinogen inhibitors known in the art.

[00768] The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function, for example, by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicylic acid or ASA), and piroxicam are preferred. Other suitable platelet inhibitory agents include IIb/IIIa antagonists (e.g., tirofiban, eptifibatide, and abciximab), thromboxane-A2-receptor antagonists (e.g., ifetroban), thromboxane-A2-synthetase inhibitors, phosphodiesterase-III (PDE-III) inhibitors (e.g., dipyridamole, cilostazol), and PDE V inhibitors (such as sildenafil), and pharmaceutically acceptable salts or prodrugs thereof.

[00769] The term anti-platelet agents (or platelet inhibitory agents), as used herein, is also intended to include ADP (adenosine diphosphate) receptor antagonists, preferably antagonists of the purinergic receptors P_2Y_1 and P_2Y_{12}, with P_2Y_{12} being even more preferred. Preferred P_2Y_{12} receptor antagonists include ticlopidine and clopidogrel, including pharmaceutically acceptable salts or prodrugs thereof. Clopidogrel is an even more preferred agent. Ticlopidine and clopidogrel are also

preferred compounds since they are known to be gentle on the gastro-intestinal tract in use. The compounds of the present invention may also be dosed in combination with aprotinin.

[00770] The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin), endothelial cell activation, inflammatory reactions, and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal alpha-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin.

[00771] The term thrombolytic (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator (TPA, natural or recombinant) and modified forms thereof, anistreplase, urokinase, streptokinase, tenecteplase (TNK), lanoteplase (nPA), factor VIIa inhibitors, PAI-I inhibitors (i.e., inactivators of tissue plasminogen activator inhibitors), alpha-2-antiplasmin inhibitors, and anisoylated plasminogen streptokinase activator complex, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

[00772] Examples of suitable anti-arrythmic agents for use in combination with the present compounds include: Class I agents (such as propafenone); Class II agents (such as carvadiol and propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as ditiazem and verapamil); K^+ channel openers such as I_{Ach} inhibitors, and I_{Kur} inhibitors (e.g., compounds such as those disclosed in WO01/40231).

[00773] The term antihypertensive agents, as used herein, include: alpha adrenergic blockers; beta adrenergic blockers; calcium channel blockers (e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil); diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone); renin inhibitors; angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril, lisinopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); angiotensin-II receptor antagonists (e.g., irbesatin, losartan, valsartan); ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265); Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389); neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual ACE/NEP inhibitors, e.g., omapatrilat, gemopatrilat, nitrates); and β-blockers (e.g., propanolol, nadolo, or carvedilol).

[00774] Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

[00775] Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include sprionolactone and eplirinone.

[00776] Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies for use in combination with the compounds of the present invention include: HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, fluvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)); squalene synthetase inhibitors; fibrates; bile acid sequestrants (such as questran); ACAT inhibitors; MTP inhibitors;

lipooxygenase inhibitors; choesterol absorption inhibitors; and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

[00777] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include: biguanides (e.g., metformin); glucosidase inhibitors (e.g., acarbose); insulins (including insulin secretagogues or insulin sensitizers); meglitinides (e.g., repaglinide); sulfonylureas (e.g., glimepiride, glyburide and glipizide); biguanide/glyburide combinations (e.g., glucovance), thiozolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in WO00/59506, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

[00778] Examples of suitable anti-depressant agents for use in combination with the compounds of the present invention include nefazodone and sertraline.

[00779] Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include: prednisone; dexamethasone; enbrel; protein tyrosine kinase (PTK) inhibitors; cyclooxygenase inhibitors (including NSAIDs, and COX-1 and/or COX-2 inhibitors); aspirin; indomethacin; ibuprofen; prioxicam; naproxen; celecoxib; and/or rofecoxib.

[00780] Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate and raloxifene.

[00781] Examples of suitable hormone replacement therapies for use in combination with the compounds of the present invention include estrogen (e.g., congugated estrogens) and estradiol.

[00782] Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include orlistat and aP2 inhibitors (such as those disclosed in WO00/59506).

[00783] Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, and hydroxyzine pamoate.

[00784] Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, and hydroxyzine pamoate.

[00785] Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, adriamycin; epithilones, cisplatin, and carboplatin.

[00786] Examples of suitable anti-ulcer and gastroesophageal reflux disease agents for use in combination with the compounds of the present invention include famotidine, ranitidine, and omeprazole.

[00787] Administration of the compounds of the present invention (i.e., a first therapeutic agent) in combination with at least one additional therapeutic agent (i.e., a second therapeutic agent), preferably affords an efficacy advantage over the compounds and agents alone, preferably while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. It is preferred that at least one of the therapeutic agents is administered in a sub-therapeutic dose. It is even more preferred that all of the therapeutic agents be administered in sub-therapeutic doses. Sub-therapeutic is intended to mean an amount of a therapeutic agent that by itself does not give the desired therapeutic effect for the condition or disease being treated. Synergistic combination is intended to mean that the observed effect of the combination is greater than the sum of the individual agents administered alone.

[00788] The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein. XIa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimentor that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays

or protocols, compounds according to the present invention could be used to test their effectiveness.

[00789] The compounds of the present invention may also be used in diagnostic assays involving thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein. For example, the presence of thrombin, Factor VIIa, IXa, Xa XIa, and/or plasma kallikrein in an unknown sample could be determined by addition of the relevant chromogenic substrate, for example S2366 for Factor XIa, to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude Factor XIa was present.

[00790] Extremely potent and selective compounds of the present invention, those having K_i values less than or equal to 0.001 μM against the target protease and greater than or equal to 0.1 μM against the other proteases, may also be used in diagnostic assays involving the quantitation of thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein in serum samples. For example, the amount of Factor XIa in serum samples could be determined by careful titration of protease activity in the presence of the relevant chromogenic substrate, S2366, with a potent and selective Factor XIa inhibitor of the present invention.

[00791] The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic and/or inflammatory disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat a thromboembolic and/or inflammatory disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or

outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

[00792] The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (e.g., for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

[00793] The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (e.g., cardboard or plastic), crates, cartons, bags (e.g., paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

[00794] The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (e.g., the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (e.g., paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (e.g., printed or applied).

DOSAGE AND FORMULATION

[00795] The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed

release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00796] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

[00797] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[00798] Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via *trans*dermal routes, using *trans*dermal skin patches. When administered in the form of a *trans*dermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[00799] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of

administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

[00800] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[00801] The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[00802] Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[00803] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

[00804] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00805] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[00806] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

[00807] Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, a standard reference text in this field.

[00808] Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of the present invention and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10

milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

[00809] Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of the present invention and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of the present invention and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

[00810] Where the compounds of the present invention are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of the present invention, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of the present invention.

[00811] Where two or more of the foregoing second therapeutic agents are administered with the compound of the present invention, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

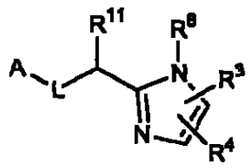
[00812] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to

minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[00813] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

What is claimed is:

1. A compound of Formula (I):



(I)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

A is C_{3-10} carbocycle substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 12-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2;

provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, or $-C(O)CH_2-$;

R^1 is, independently at each occurrence, $-NH_2$, $-NH(C_1-C_3$ alkyl), $-N(C_1-C_3$ alkyl$)_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7CO_2R^a$, $-CH_2NH_2$, $-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl$)_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(C_1-C_3$ alkyl), $-CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $-CH(C_{1-4}$ alkyl$)NH_2$, $-C(C_{1-4}$ alkyl$)_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3,

$-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-cyclopropyl, or C_{1-6} alkyl substituted with 0-1 R^{1a};

R^{1a} is H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

R^2 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{2a}, C_{2-6} alkenyl substituted with 0-2 R^{2a}, C_{2-6} alkynyl substituted with 0-2 R^{2a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{2b}, or $-(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{2b};

R^{2a} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

R^{2b} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

alternately, when R^1 and R^2 groups are substituted on adjacent ring atoms, they can be taken together with the ring atoms to which they are attached to form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said carbocycle or heterocycle is substituted with 0-2 R^{2b};

R^3 is $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$,

$-(CH_2)_r-CO_2R^{3b}$, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r-$5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

R^{3a} is, independently at each occurrence, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, -C(O)-C_1-C_4 alkyl, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, C_{1-6} alkyl substituted by R^{3d}, C_{2-6} alkenyl substituted by R^{3d}, C_{2-6} alkynyl substituted by R^{3d}, C_{3-6} cycloalkyl substituted by 0-1 R^{3d}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r-$5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

alternately, when two R^{3a} groups are located on adjacent atoms, they can be taken together with the atoms to which they are attached to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

R^{3b} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r-$5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

R^{3c} is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{3d}, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

R^{3d} is, independently at each occurrence, H, =O, -$(CH_2)_r$$OR^a$, F, Cl, Br, CN, NO_2, -$(CH_2)_r$$NR^7R^8$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -$NR^7C(O)R^b$, -$C(O)NR^8R^9$, -$SO_2NR^8R^9$, -$NR^8SO_2NR^8R^9$, -$NR^8SO_2R^c$, -$S(O)_pR^c$, -$(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, C_{2-6} alkynyl substituted with 0-2 R^e, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_pR^c$, -$S(O)R^c$, -$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{4b}, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

R^{4a} is, independently at each occurrence, H, F, =O, C_{1-6} alkyl, OR^a, SR^a, CF_3, CN, NO_2, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_2R^c$, -$S(O)R^c$, or -$S(O)_2R^c$;

R^{4b} is, independently at each occurrence, H, =O, =NR^8, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, -SO_2R^c, -NR^7R^8, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

alternately, R^3 and R^4 groups when located on adjacent atoms, can be taken together to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

R^6 is H;

R^7 is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n-C_{3-10}$ carbocycle, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{1-4}$ alkyl), or $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{6-10}$ aryl); wherein said alkyl, carbocycle, heteroaryl, and aryl are optionally substituted with 0-2 R^f;

R^8 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_r$-phenyl, or $-(CH_2)_n$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said alkyl, phenyl and heterocycle are optionally substituted with 0-2 R^f;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

R^{8a} is, independently at each occurrence, H, OH, C_{1-6} alkyl, C_{1-4} alkoxy, $(C_{6-10}$ aryl)-C_{1-4} alkoxy, $-(CH_2)_n$-phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{1-4}$ alkyl), or $-C(O)O-(C_{1-4}$ alkyl)$OC(O)-(C_{6-10}$ aryl); wherein said phenyl, aryl, and heteroaryl is optionally substituted with 0-2 R^f;

R^9 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_r$ -phenyl; wherein said alkyl and phenyl are optionally substituted with 0-2 R^f;

R^{9a} is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

alternatively, R^8 and R^9, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional

heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, C_{2-6} alkenyl substituted with 0-3 R^{10a}, C_{2-6} alkynyl substituted with 0-3 R^{10a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

R^{10a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$-, $-S(O)R^c$, or $-S(O)_2R^c$;

R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CR^{14}R^{15})_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CR^{14}R^{15})_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b};

R^{11a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, CF_3, SR^a, F, CN, NO_2, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^c$, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^d;

R^{11b} is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-,

$-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R^g;

R^{14} and R^{15} are, independently at each occurrence, H, F, or C_{1-4} alkyl;

alternately, R^{14} combines with R^{15} to form =O;

R^a is, independently at each occurrence, H, CF_3, C_{1-6} alkyl, $-(CH_2)_r-C_{3-7}$ cycloalkyl, $-(CH_2)_r-C_{6-10}$ aryl, or $-(CH_2)_r$-5- to 10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said cycloalkyl, aryl and heterocycle groups are optionally substituted with 0-2 R^f;

R^b is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

R^c is, independently at each occurrence, CF_3, C_{1-6} alkyl substituted with 0-2 R^f, C_{3-6} cycloalkyl substituted with 0-2 R^f, C_{6-10} aryl, 5- to 10-membered heteroaryl, (C_{6-10} aryl)-C_{1-4} alkyl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl, wherein said aryl and heteroaryl groups are optionally substituted with 0-3 R^f;

R^d is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, or

C_{2-6} alkynyl substituted with 0-2 R^e;

R^e is, independently at each occurrence, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-C_{1-4} alkyl, $-NR^8SO_2CF_3$, $-NR^8SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

R^f is, independently at each occurrence, H, =O, $-(CH_2)_r-OR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-C_{1-4} alkyl, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-(CH_2)_n$-phenyl;

R^g is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

s, at each occurrence, is selected from 1, 2; 3, and 4;

provided that:

(a). when L is –C(O)NH-, R^3 is not 2,4-dichlorophenyl, 4-nitrophenyl or pentafluorophenyl;

(b). when L is –C(O)NH-, R^{11} is not $-CH_2$-(3-indolyl), $-(CH_2)_4NHCO_2(t\text{-Bu})$ or $-(CH_2)_4NH_2$.

2. A compound according to Claim 1, wherein:

L is $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, $-CH_2CONR^{10}$-, or $-NR^{10}COCH_2$-;

R^3 is $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5-10 membered heterocycle comprising:

carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, $-(CH_2)_r$-phenyl substituted with 0-2 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

R^{11} is C_{1-4} haloalkyl, $-(CH_2)_r-CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{11a}, C_{2-6} alkenyl substituted with 0-2 R^{11a}, C_{2-6} alkynyl substituted with 0-2 R^{11a}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{11b}, or $-(CH_2)_r$-5-to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

3. A compound according to Claim 1, wherein:

R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, -NHEt, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, -C(O)NHMe, -C(O)NHBn, $-(CH_2)_r$-phenyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, naphthyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, indanyl substituted with 0-2

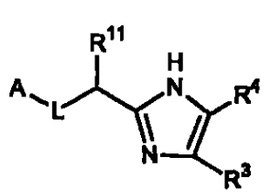
R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a} and 0-1 R^{3d};

R^4 is H, F, Cl, Br, CF_3, OMe, NH_2, CO_2H, CO_2Me, CO_2Et, -$CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, -$CH_2CH_2CO_2H$, -$CH_2CH_2CO_2Me$, -$CH_2CH_2CO_2Et$, -$CH_2CH_2CONH_2$, or -$CH_2CH_2CONHCH_2CH_2Ph$; and

R^{11} is C_{1-6} alkyl, -$CH_2CONR^8R^9$, -$CH_2CH_2CONR^8R^9$, -CH_2OBn, -CH_2SBn, -$(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{11b}.

4. A compound according to Claim 1, wherein the compound is of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl,

2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

L is -C(O)NH- or -NHC(O)-;

R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, -C(O)NHMe, -C(O)NHBn, phenyl substituted with 0-2 R^{3a}, naphthyl substituted with 0-2 R^{3a}, indanyl substituted with 0-2 R^{3a}, or a 5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a};

R^4 is H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{4b};

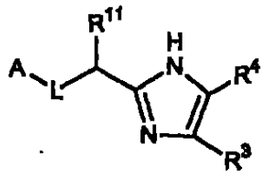
R^{11} is C_{1-6} alkyl, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or $-(CH_2)_r$-5- to 10-membered heteroaryl substituted with 0-2 R^{11b} and selected from thiazolyl, oxazolyl, triazolyl, tetrazolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl; and

R^{11b} is, independently at each occurrence, H, F, Cl, Br, CF_3, OMe, OEt, $O(i\text{-Pr})$, OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, C_1-C_4-alkyl, Ph, or Bn;

alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-

membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R8.

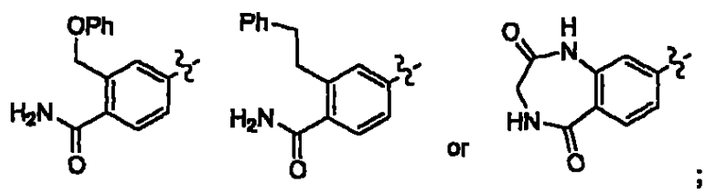
5. A compound according to Claim 1, wherein the compound is of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

A is 4-CH_2NH_2-cyclohexyl, 4-CO_2Me-cyclohexyl, 4-$CONH_2$-cyclohexyl, 4-$NHCO_2$(*t*-Bu)-cyclohexyl, 4-$NHCO_2$Bn-cyclohexyl, phenyl, 4-Me-phenyl, 3-OMe-phenyl, 4-CH_2NH_2-phenyl, 3-$CONH_2$-phenyl, 4-$CONH_2$-phenyl, 3-amidino-phenyl, 4-amidino-phenyl, 2-F-4-Me-phenyl, 2-Bn-4-CH_2NH_2-phenyl, 4-SO_2NH_2-phenyl, 2-F-5-OMe-phenyl, 2-F-4-Cl-phenyl, 2-F-4-CH_2NH_2-phenyl, 2-F-4-$CONH_2$-phenyl, 2-Cl-4-$CONH_2$-phenyl, 2-Et-4-CH_2NH_2-phenyl, 2-NHEt-4-CH_2NH_2-phenyl, 2-OMe-4-$CONH_2$-phenyl, 3-OMe-4-$CONH_2$-phenyl, 1,2,3,4-tetrahydronaphth-2-yl, 3-Cl-thien-2-yl, indol-5-yl, indol-6-yl, indazol-6-yl, 3-NH_2-indazol-6-yl, 3-NH_2-indazol-5-yl, 1-Me-3-NH_2-indazol-6-yl, 3-NH_2-benzisoxazol-6-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 2-COPh-1,2,3,4-tetrahydroisoquinolin-3-yl, 2-CO_2Bu-1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-1-on-6-yl, 2H-isoquinolin-1-on-6-yl, isoquinolin-6-yl, 1-NH_2-isoquinolin-6-yl, 1-NH_2-3-Me-isoquinolin-6-yl, 1-NH_2-5,6,7,8-tetrahydroisoquinolin-6-yl, 4-NH_2-quinazolin-7-yl, 3H-quinazolin-4-on-7-yl,



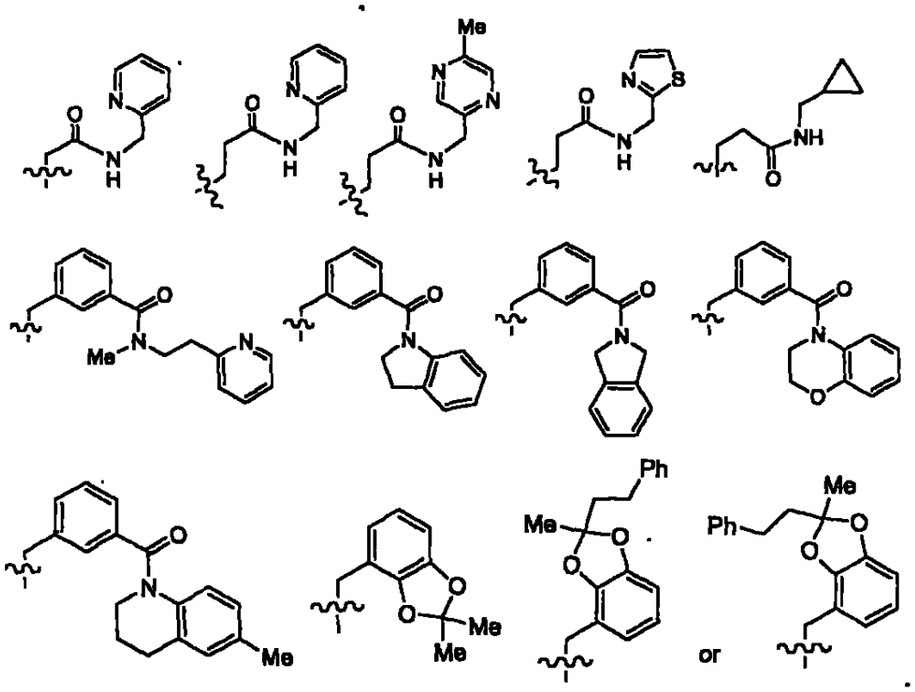
;

R^3 is CO_2H, CO_2Me, -C(O)NHCH$_2$CO$_2$H, -C(O)NHCH$_2$CO$_2$Et, -C(O)NH$_2$, -C(O)NHMe, -C(O)NHBn, phenyl, phenethyl, -(CH=CH)-phenyl, 3-biphenyl, 4-biphenyl, 3,4-methylenedioxyphenyl, 1-naphthyl, 2-naphthyl, 3-NH$_2$-phenyl, 3-NMe$_2$-phenyl, 4-OPh-phenyl, 4-OBn-phenyl, 4-(*t*-butoxymethyl)-phenyl, 4-SO_2Me-phenyl, 3-CN-phenyl, 4-CN-phenyl, 3-F-phenyl, 4-F-phenyl, 3-Cl-phenyl, 4-Cl-phenyl, 3-Br-phenyl, 4-Br-phenyl, 3-OH-phenyl, 4-OH-phenyl, 2-OMe-phenyl, 3-OMe-phenyl, 4-OMe-phenyl, 3-CF_3-phenyl, 4-CF_3-phenyl, 3-CO_2H-phenyl, 4-CO_2H-phenyl, 3-CO_2Me-phenyl, 4-CO_2Me-phenyl, 3-CH$_2$CO$_2$H-phenyl, 4-CH$_2$CO$_2$H-phenyl, 4-CH$_2$CO$_2$Me-phenyl, 3-CH$_2$CO$_2$Et-phenyl, 4-CH$_2$CO$_2$Et-phenyl, 3-CONH$_2$-phenyl, 4-CONH$_2$-phenyl, 3-CH$_2$CONH$_2$-phenyl, 4-CH$_2$CONH$_2$-phenyl, 4-CONHMe-phenyl, 4-CONMe$_2$-phenyl, 4-amidino-phenyl, 3-NHCOMe-phenyl, 4-NHCOMe-phenyl, 4-NHCO$_2$Me-phenyl, 4-SO_2NH_2-phenyl, 3-NHSO$_2$Me-phenyl, 4-NHSO$_2$Me-phenyl, 2,4-diF-phenyl, 3-F-4-CN-phenyl, 3-CN-5-F-phenyl, 3-F-4-CONH$_2$-phenyl, 3-CO_2H-4-CN-phenyl, 3-NMe$_2$-4-CN-phenyl, 3-Ph-4-CONH$_2$-phenyl, 4-(2-oxo-1-piperidino)-phenyl, thiazol-2-yl, 4-CO_2Me-thiazol-2-yl, 4-CONH$_2$-thiazol-2-yl, 1-Bn-pyazol-4-yl, 5-Ph-oxazol-2-yl, 5-CONH$_2$-thien-2-yl, 5-CO_2H-thien-2-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 6-NH$_2$-pyrid-3-yl, benzimidazol-2-yl, 1-Me-benzimidazol-2-yl, benzoxazol-2-yl, benzothiazol-2-yl, 3-NH$_2$-benzisoxazol-6-yl, 3-NH$_2$-benzisoxazol-5-yl, indazol-5-yl, indazol-6-yl, 3-NH$_2$-indazol-5-yl, 3-OH-indazol-5-yl, 3-NH$_2$-indazol-6-yl, 3-NH$_2$-4-F-indazol-6-yl, 3-NH$_2$-5-F-indazol-6-yl, 3-NH$_2$-7-F-indazol-6-yl, 4-imino-3,4-dihydro-2*H*-phthalazin-1-on-7-yl, 3-(5-tetrazolyl)-phenyl, 2,3-dihydro-isoindol-1-on-6-yl, quinolin-5-yl, quinolin-6-yl, quinolin-8-yl, isoquinolin-5-yl, 2H-isoquinolin-1-on-6-yl, 2,4-diaminoquinazolin-7-yl, or 4-NH$_2$-quinazolin-7-yl;

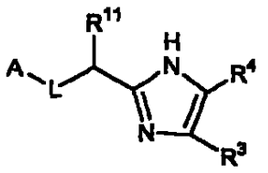
R^4 is H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, phenyl, 3-F-4-CN-phenyl, or 3-NH$_2$-6-indazolyl; and

R^{11} is Me, neopentyl, cyclohexylmethyl, -CH$_2$CH$_2$CONHBn,

-$CH_2CH_2CONH(CH_2CH_2Ph)$, -$CH_2CH_2CON(Me)Bn$, benzyl, phenethyl, 2-Me-benzyl, 3-Me-benzyl, 4-Me-benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl, 2-Cl-benzyl, 3-Cl-benzyl, 4-Cl-benzyl, 2-Br-benzyl, 3-Br-benzyl, 4-Br-benzyl, 3-CF_3-benzyl, 4-CF_3-benzyl, 2-NH_2-benzyl, 3-NH_2-benzyl, 2-NO_2-benzyl, 3-NO_2-benzyl, 4-NO_2-benzyl, 3-OMe-benzyl, 4-OMe-benzyl, 3-OCF_2H-benzyl, 2-OCF_3-benzyl, 3-OCF_3-benzyl, 2-OPh-benzyl, 3-OPh-benzyl, 2-OBn-benzyl, 3-OBn-benzyl, 4-OBn-benzyl, 4-COPh-benzyl, 3-CO_2H-benzyl, 3-CO_2Me-benzyl, 3-NHAc-benzyl, 2-NHCOPh-benzyl, 2-NHCOBn-benzyl, 3-NHCOBn-benzyl, 3-N(Me)COPh-benzyl, 3-(-$NHCOCH_2CH_2Ph$)-benzyl, 2-$NHSO_2Ph$-benzyl, 3-$NHSO_2Ph$-benzyl, 3-[$SO_2N(Me)Ph$]-benzyl, 3-[$N(Me)SO_2Ph$]-benzyl, 3-[CONH(*i*-Bu)]-benzyl, 3-[CONH(*t*-Bu)]-benzyl, 3-[CONH(isopentyl)]-benzyl, 3-[CONH(2-Me-Ph)]-benzyl, 3-[CONH(3-Me-Ph)]-benzyl, 3-[CONH(4-Me-Ph)]-benzyl, 3-[CONH(4-F-Ph)]-benzyl, 3-[CONH(1-naphthyl)]-benzyl, 3-(CONHBn)-benzyl, 3-[CONH(4-Cl-Bn)]-benzyl, 3-[CONH(4-OMe-Bn)]-benzyl, 3-[$CONHCH_2CH_2Ph$]-benzyl, 3-[$CONHCH_2CH_2$(4-OMe-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(2-Cl-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(3-Cl-Ph)]-benzyl, 3-[$CONHCH_2CH_2$(4-Cl-Ph)]-benzyl, 3-[$CONH(CH_2)_3Ph$]-benzyl, 3-[$CONMe_2$]-benzyl, 3-[CON(Me)(Et)]-benzyl, 3-[CON(Me)(*i*-Pr)]-benzyl, 3-[CON(Me)(*i*-Bu)]-benzyl, 3-[CON(Me)Ph]-benzyl, 3-[CON(Me)(3-Me-Ph)]-benzyl, 3-[CON(Me)(4-Me-Ph)]-benzyl, 3-[CON(Me)Bn]-benzyl, 3-[CON(Me)(3-Cl-Bn)]-benzyl, 3-[CON(Me)(4-Cl-Bn)]-benzyl, 3-[$CON(Me)(CH_2CH_2Ph)$]-benzyl, 3-[CON(Et)Ph]-benzyl, 3-[CO(1-piperidino)]-benzyl, 3-[CO(4-Ph-1-piperidino)]-benzyl, 3-[CO(1,2,3,4-tetrahydroisoquinolino)]-benzyl, 2-Ph-benzyl, 3-Ph-benzyl, 4-Ph-benzyl, 3-phenethyl-benzyl, -CH_2OBn, -CH_2SBn, 1-naphthylmethyl, 2-naphthylmethyl, thiazol-4-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, 1-Bn-imidazol-4-ylmethyl, benzothiazol-2-ylmethyl,



6. A compound according to Claim 1, wherein the compound is of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

R^3 is 3-NH_2-indazol-5-yl, 3-OH-indazol-5-yl, 3-NH_2-benzisoxazol-6-yl, 3-NH_2-benzisoxazol-5-yl, indazol-5-yl, indazol-6-yl, 3-NH_2-indazol-6-yl, 3-NH_2-4-F-indazol-6-yl, 3-NH_2-5-F-indazol-6-yl, 3-NH_2-7-F-indazol-6-yl, isoquinolin-5-yl, quinolin-5-yl, quinolin-8-yl, 2H-isoquinolin-1-on-6-yl, 2,4-diaminoquinazolin-7-yl, or 4-NH_2-quinazolin-7-yl.

7. A compound according to Claim 6, wherein:

L is -C(O)NR^{10}- or -NR^{10}C(O)-;

R^1 is, independently at each occurrence, F, Cl, Me, Et, -NH$_2$, -C(=NH)NH$_2$, -C(O)NH$_2$, -CH$_2$NH$_2$, -CH$_2$CH$_2$NH$_2$, -CH$_2$NHCO$_2$Bn, -CH$_2$NHCO$_2$(*t*-Bu), -CH(Me)NH$_2$, -C(Me)$_2$NH$_2$, -NHEt, -NHCO$_2$(*t*-Bu), -NHCO$_2$Bn, -SO$_2$NH$_2$, OR^a, or -CH$_2$R^{1a};

R^4 is H, F, Cl, Br, OMe, NH$_2$, CF$_3$, CO$_2$H, CO$_2$Me, CO$_2$Et, -CONR^{8}R^9, C$_{1-6}$ alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and S(O)$_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, -CH$_2$CH$_2$CO$_2$H, -CH$_2$CH$_2$CO$_2$Me, -CH$_2$CH$_2$CO$_2$Et, -CH$_2$CH$_2$CONH$_2$, or -CH$_2$CH$_2$CONHCH$_2$CH$_2$Ph;

R^{11} is C$_1$-C$_6$ alkyl, -CH$_2$CONR^{8}R^9, -CH$_2$CH$_2$CONR^{8}R^9, -CH$_2$OBn, -CH$_2$SBn, -(CH$_2$)$_r$-C$_{3-7}$ cycloalkyl substituted with 0-2 R^{11b}, -(CH$_2$)$_r$-phenyl substituted with 0-2 R^{11b}, -(CH$_2$)$_r$-naphthyl substituted with 0-2 R^{11b}, or -(CH$_2$)$_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and S(O)$_p$, wherein said heterocycle is substituted with 0-2 R^{11b}; and

R^{11b} is, independently at each occurrence, H, F, Cl, Br, CF$_3$, OMe, OEt, O(*i*-Pr), OCF$_3$, OCHF$_2$, CN, OPh, OBn, NO$_2$, -NH$_2$, -C(O)R^a, -C(O)OR^a, -C(O)NR^{7}R^8, -NR^{7}C(O)R^b, -N^{8}CO$_2$R^c, -S(O)$_p$NR^{8}R^9, -NR^{8}S(O)$_p$R^c, -SO$_2$R^c, C$_1$-C$_4$-alkyl, Ph, or Bn.

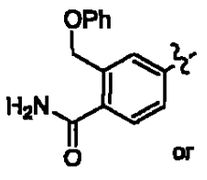
8. A compound according to Claim 7, wherein:

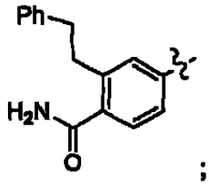
A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl; and

R^{10} is H.

9. A compound according to Claim 8, wherein:

A is 4-CH_2NH_2-cyclohexyl, 4-CO_2Me-cyclohexyl, 4-$CONH_2$-cyclohexyl, 4-$NHCO_2$(*t*-Bu)-cyclohexyl, 4-$NHCO_2$Bn-cyclohexyl, phenyl, 4-Me-phenyl, 3-OMe-phenyl, 4-CH_2NH_2-phenyl, 3-$CONH_2$-phenyl, 4-$CONH_2$-phenyl, 3-amidino-phenyl, 4-amidino-phenyl, 2-F-4-Me-phenyl, 2-Bn-4-CH_2NH_2-phenyl, 4-SO_2NH_2-phenyl, 2-F-5-OMe-phenyl, 2-F-4-Cl-phenyl, 2-F-4-CH_2NH_2-phenyl, 2-F-4-$CONH_2$-phenyl, 2-Cl-4-$CONH_2$-phenyl, 2-Et-4-CH_2NH_2-phenyl, 2-NHEt-4-CH_2NH_2-phenyl, 2-OMe-4-$CONH_2$-phenyl, 3-OMe-4-$CONH_2$-phenyl, 1,2,3,4-tetrahydronaphth-2-yl, 3-Cl-thien-2-yl, indol-5-yl, indol-5-yl, indazol-5-yl, indazol-6-yl, 3-NH_2-indazol-6-yl, 3-NH_2-indazol-5-yl, 1-Me-3-NH_2-indazol-6-yl, 3-NH_2-benzisoxazol-6-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 2-COPh-1,2,3,4-tetrahydroisoquinolin-3-yl, 2-CO_2Bn-1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-totrahydroisoquinolin-1-on-6-yl, 2H-isoquinolin-1-on-6-yl, isoquinolin-6-yl, 1-NH_2-isoquinolin-6-yl, 1-NH_2-3-Me-isoquinolin-6-yl, 1-NH_2-5,6,7,8-tetrahydroisoquinolin-6-yl, 4-NH_2-quinazolin-7-yl, 3H-quinazolin-4-on-7-yl,



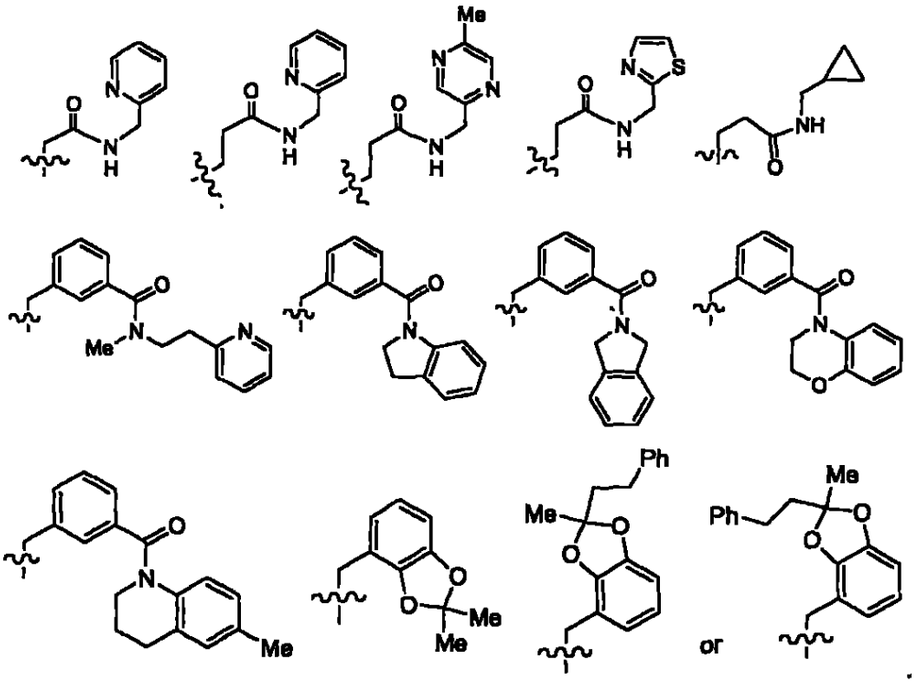
or


;

R^4 is H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, phenyl, 3-F-4-CN-phenyl, or 3-NH_2-6-indazolyl; and

R^{11} is Me, neopentyl, cyclohexylmethyl, -$CH_2CH_2CONHBn$, -$CH_2CH_2CONH(CH_2CH_2Ph)$, -$CH_2CH_2CON(Me)Bn$, benzyl, phenethyl, 2-Me-benzyl, 3-Me-benzyl, 4-Me-benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl, 2-Cl-benzyl, 3-Cl-benzyl, 4-Cl-benzyl, 2-Br-benzyl, 3-Br-benzyl, 4-Br-benzyl, 3-CF_3-benzyl, 4-CF_3-benzyl, 2-NH_2-benzyl, 3-NH_2-benzyl, 2-NO_2-benzyl, 3-NO_2-benzyl, 4-NO_2-benzyl, 3-OMe-benzyl, 4-OMe-benzyl, 3-OCF_2H-benzyl, 2-OCF_3-benzyl, 3-OCF_3-benzyl, 2-OPh-benzyl, 3-OPh-benzyl, 2-OBn-benzyl, 3-OBn-benzyl, 4-OBn-benzyl, 4-COPh-benzyl, 3-CO_2H-benzyl, 3-CO_2Me-benzyl, 3-NHAc-benzyl, 2-NHCOPh-benzyl, 2-NHCOBn-benzyl, 3-NHCOBn-benzyl, 3-N(Me)COPh-benzyl, 3-(-$NHCOCH_2CH_2Ph$)-benzyl, 2-$NHSO_2Ph$-benzyl, 3-$NHSO_2Ph$-benzyl, 3-[$SO_2N(Me)Ph$]-benzyl, 3-[$N(Me)SO_2Ph$]-benzyl, 3-[CONH(*i*-Bu)]-benzyl, 3-[CONH(*t*-Bu)]-benzyl, 3-[CONH(isopentyl)]-benzyl, 3-[CONH(2-Me-Ph)]-benzyl, 3-[CONH(3-Me-Ph)]-benzyl, 3-[CONH(4-Me-Ph)]-benzyl, 3-[CONH(4-F-Ph)]-benzyl, 3-[CONH(1-naphthyl)]-benzyl, 3-(CONHBn)-benzyl, 3-[CONH(4-Cl-Bn)]-benzyl, 3-[CONH(4-OMe-Bn)]-benzyl, 3-[$CONHCH_2CH_2Ph$]-benzyl, 3-[$CONHCH_2CH_2(4\text{-}OMe\text{-}Ph)$]-benzyl, 3-[$CONHCH_2CH_2(2\text{-}Cl\text{-}Ph)$]-benzyl, 3-[$CONHCH_2CH_2(3\text{-}Cl\text{-}Ph)$]-benzyl, 3-[$CONHCH_2CH_2(4\text{-}Cl\text{-}Ph)$]-benzyl, 3-[$CONH(CH_2)_3Ph$]-benzyl, 3-[$CONMe_2$]-benzyl, 3-[CON(Me)(Et)]-benzyl, 3-[CON(Me)(*i*-Pr)]-benzyl, 3-[CON(Me)(*i*-Bu)]-benzyl, 3-[CON(Me)Ph]-benzyl, 3-[CON(Me)(3-Me-Ph)]-benzyl, 3-[CON(Me)(4-Me-Ph)]-benzyl, 3-[CON(Me)Bn]-benzyl, 3-[CON(Me)(3-Cl-Bn)]-benzyl, 3-[CON(Me)(4-Cl-Bn)]-benzyl, 3-[$CON(Me)(CH_2CH_2Ph)$]-benzyl, 3-[CON(Et)Ph]-benzyl, 3-[CO(1-piperidino)]-benzyl, 3-[CO(4-Ph-1-piperidino)]-benzyl, 3-[CO(1,2,3,4-tetrahydroisoquinolino)]-benzyl, 2-Ph-benzyl, 3-Ph-benzyl, 4-Ph-benzyl, 3-phenethyl-benzyl, -CH_2OBn, -CH_2SBn, 1-naphthylmethyl, 2-naphthylmethyl, thiazol-4-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, 1-Bn-imidazol-4-ylmethyl,

benzothiazol-2-ylmethyl,



5

10. A compound according to Claim 8, wherein:

A is 4-CH_2NH_2-cyclohexyl, 4-$NHCO_2$(*t*-Bu)-cyclohexyl, 4-$NHCO_2$Bn-cyclohexyl, or 1-NH_2-5,6,7,8-tetrahydroisoquinolin-6-yl;

L is –C(O)NH- or NHC(O)-;

R^3 is indazol-5-yl, indazol-6-yl, 3-NH_2-indazol-5-yl, 3-OH-indazol-5-yl, 3-NH_2-indazol-6-yl, 3-NH_2-4-F-indazol-6-yl, 3-NH_2-5-F-indazol-6-yl, 3-NH_2-7-F-indazol-6-yl, or 4-NH_2-quinazolin-7-yl;

R^4 is H, Me, F, Br, Cl, or CF_3; and

R^{11} is benzyl substituted with 0-2 R^{11b}.

10

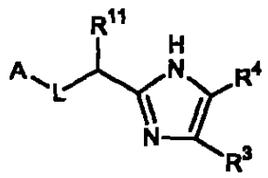
11. A compound according to Claim 10, wherein:

A is 4-CH_2NH_2-cyclohexyl;

L is –C(O)NH-; and

R^3 is 3-NH_2-indazol-6-yl or 4-NH_2-quinazolin-7-yl.

12. A compound according to Claim 1, wherein the compound is of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

A is substituted with 0-2 R^1 and 0-1 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

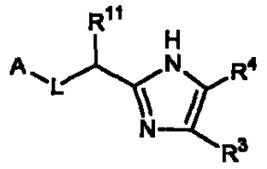
L is $-C(O)NR^{10}-$ or $-NR^{10}C(O)-$;

R^3 is $-(CH_2)_r-$5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

R^4 is H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, $-CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b}; and

R^{11} is benzyl substituted with 0-2 R^{11b}.

13. A compound according to Claim 1, wherein the compound is of Formula (II):



(II)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

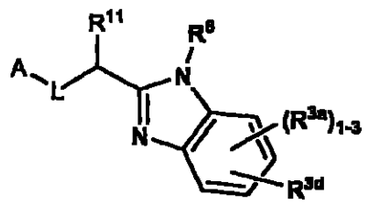
L is $-C(O)NR^{10}-$ or $-NR^{10}C(O)-$;

R^3 is $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d};

R^4 is, independently at each occurrence, H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, phenyl, 3-F-4-CN-phenyl, or 3-NH_2-6-indazolyl; and

R^{11} is benzyl substituted with 0-2 R^{11b}.

14. A compound according to Claim 1, wherein the compound is of Formula (III):



(III)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

R^{3a} is, independently at each occurrence, =O, F, Cl, Br, Me, CN, OH, NH_2, OMe, O(*t*-Bu), OBn, CF_3, CO_2H, CO_2Me, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, -NHCOMe, $-CONH_2$, $-CH_2CONH_2$, -CONHMe, $-CONMe_2$, $-C(=NH)NH_2$, $-NR^7R^8$, $-SO_2Me$, $-SO_2NH_2$, Ph, or 2-oxo-piperidin-1-yl;

R^{3d} is H or C_{1-4} alkyl;

R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, $-(CH_2)_r$-phenyl substituted with 0-2 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

R^{11} is C_{1-4} haloalkyl, $-(CH_2)_r-CONR^8R^9$, C_{1-6} alkyl substituted with 0-2 R^{11a}, C_{2-6} alkenyl substituted with 0-2 R^{11a}, C_{2-6} alkynyl substituted with 0-2 R^{11a}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

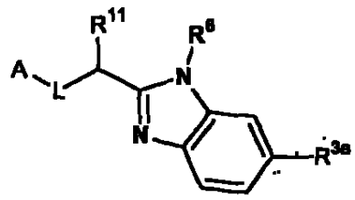
15. A compound according to Claim 14, wherein:

R^1 is, independently at each occurrence, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, or $-CH_2CH_2NH_2$;

R^{10} is H, Me, benzyl, or phenethyl; and

R^{11} is Me, -$(CH_2)_r$-phenyl substituted with 0-1 R^{11b}, or -$(CH_2)_r$-5-10 membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^{11b}.

16. A compound according to Claim 1, wherein the compound is of Formula (IV):



(IV)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

A is cyclohexyl substituted with 1 R^1, phenyl substituted with 1 R^1, pyridyl substituted with 1 R^1, naphthyl substituted with 1 R^1, benzisoxazole substituted with 1 R^1, or isoquinolinyl substituted with 0-1 R^1;

L is -C(O)NH-, -C(O)NMe-, -C(O)N(benzyl)-, -C(O)N(phenethyl)-, -NHC(O)-, -CH_2C(O)NH-, -NHC(O)CH_2-, -C(O)NHCH_2-, or -NHC(O)CH_2-;

R^1 is, independently at each occurrence, -NH_2, -C(=NH)NH_2, -C(O)NH_2, or -CH_2NH_2;

R^{3a} is F, Cl, Br, Me, CN, OMe, CF_3, CO_2H, CO_2Me, CO_2Et, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, $CONH_2$, -CONHMe, -CON(Me)2, -CH_2CONH_2, or -C(=NH)NH_2;

R^6 is H;

R^{10} is H, Me, benzyl, or phenethyl; and

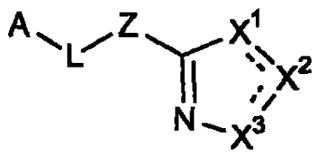
R^{11} is Me, -$(CH_2)_r$-phenyl substituted with 0-1 R^{11b}, or -$(CH_2)_r$-5-10 membered heteroaryl substituted with 0-1 R^{11b} and selected from thiazolyl, imidazolyl, pyridyl, and benzothiazolyl.

17. A compound according to Claim 16, wherein:

A is 4-CH_2NH_2-cyclohexyl or 4-amidino-phenyl; and

R^{3a} is, independently at each occurrence, CO_2H, CO_2Me, $-CH_2CO_2H$, $-CH_2CO_2Et$, $-CONH_2$, or $-CH_2CONH_2$.

18. A compound of Formula (V):

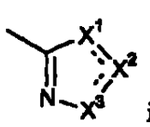
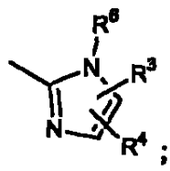


(V)

or its stereoisomers, tautomers, a pharmaceutically acceptable salts, or solvates thereof, wherein:

A is C_{3-10} carbocycle substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 12-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2; provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

X^1, X^2, and X^3 are independently CR^3, CR^4, CR^4R^5, O, $S(O)_p$, N, NR^3, NR^6, or C(O); provided that no S-S, S-O, or O-O bond is present in the ring;

provided that  is other than  ;

Z is $-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-(CH_2)-$, $-NR^{13}-$, or $-NR^{13}CH_2-$;

L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$,

$-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, or $-C(O)CH_2-$;

R^1 is, independently at each occurrence, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7C(O)OR^a$, $-CH_2NH_2$, $-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl$)_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(C_{1-3}$ alkyl), $-CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $-CH(C_{1-4}$ alkyl$)NH_2$, $-C(C_{1-4}$ alkyl$)_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-cyclopropyl, or C_{1-6} alkyl substituted with 0-1 R^{1a};

R^{1a} is H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p-C_{1-4}$ alkyl, $-S(O)_p$-phenyl, or $-(CF_2)_rCF_3$;

R^2 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{2a}, C_{2-6} alkenyl substituted with 0-2 R^{2a}, C_{2-6} alkynyl substituted with 0-2 R^{2a}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{2b}, or $-(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{2b};

R^{2a} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

R^{2b} is, independently at each occurrence, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

alternately, when R^1 and R^2 groups are substituted on adjacent ring atoms, they can be taken together with the ring atoms to which they are attached to form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said carbocycle or heterocycle is substituted with 0-2 R^{2b};

R^3 is, independently at each occurrence, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

R^{3a} is, independently at each occurrence, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-C(O)$-C_{1-4} alkyl, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, C_{1-6} alkyl substituted by R^{3d}, C_{2-6} alkenyl substituted by R^{3d}, C_{2-6} alkynyl substituted by R^{3d}, C_{3-6} cycloalkyl substituted by 0-1 R^{3d}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{3d}, or

$-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

alternately, when two R^{3a} groups are located on adjacent atoms, they can be taken together with the atoms to which they are attached to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

R^{3b} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

R^{3c} is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^{3d}, C_{2-6} alkenyl substituted with 0-2 R^{3d}, C_{2-6} alkynyl substituted with 0-2 R^{3d}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^{3d}, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3d};

R^{3d} is, independently at each occurrence, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_pR^c$, $-(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, C_{2-6} alkynyl substituted with 0-2 R^e, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

R^4 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{4b}, or $-(CH_2)_r$–5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

R^{4a} is, independently at each occurrence, H, F, =O, C_{1-6} alkyl, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$,$-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

R^{4b} is, independently at each occurrence, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

alternately, R^3 and R^4 groups when located on adjacent atoms, can be taken together to form a C_{3-10} carbocycle substituted with 0-2 R^{3d} or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3d};

R^5 is, independently at each occurrence, H, F, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{5a}, C_{2-6} alkenyl substituted with 0-2 R^{5a}, C_{2-6} alkynyl substituted with 0-2 R^{5a}, $-(CH_2)_r$–C_{3-10} carbocycle substituted with 0-3 R^{5b}, or $-(CH_2)_r$–5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{5b};

R^{5a} is, independently at each occurrence, H, =O, OR^a, SR^a, F, Cl, Br, I, CF_3, OCF_3, CN, NO_2, $-NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, or $-S(O)_2R^c$;

R^{5b} is, independently at each occurrence, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy-;

R^6 is, independently at each occurrence, H, C_{1-6} alkyl, C_{1-4} haloalkyl, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, $-S(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^7 is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n$-C_{3-10} carbocycle, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O$-(C_{1-4} alkyl)$OC(O)$-(C_{1-4} alkyl), or $-C(O)O$-(C_{1-4} alkyl)$OC(O)$-(C_{6-10} aryl); wherein said alkyl, carbocycle, heteroaryl, and aryl are optionally substituted with 0-2 R^f;

R^8 is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_r$-phenyl, or $-(CH_2)_n$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said alkyl, phenyl and heterocycle are optionally substituted with 0-2 R^f;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

R^{8a} is, independently at each occurrence, H, OH, C_{1-6} alkyl, C_{1-4} alkoxy, (C_{6-10} aryl)-C_{1-4} alkoxy, $-(CH_2)_n$-phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O$-(C_{1-4} alkyl)$OC(O)$-(C_{1-4} alkyl), or

-C(O)O-(C_{1-4} alkyl)OC(O)-(C_{6-10} aryl); wherein said phenyl, aryl, and heteroaryl is optionally substituted with 0-2 R^f;

R^9 is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl; wherein said alkyl and phenyl are optionally substituted with 0-2 R^f;

R^{9a} is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl;

alternatively, R^8 and R^9, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising carbon atoms and 0-2 additional heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d;

R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, C_{2-6} alkenyl substituted with 0-3 R^{10a}, C_{2-6} alkynyl substituted with 0-3 R^{10a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

R^{10a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, SR^a, F, CF_3, CN, NO_2, -$C(O)OR^a$, -NR^7R^8, -$C(O)NR^7R^8$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8SO_2R^c$-, -$S(O)R^c$, or -$S(O)_2R^c$;

R^{11} is C_{1-4} haloalkyl, -$(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, -$(CR^{14}R^{15})_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or

-$(CR^{14}R^{15})_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b};

R^{11a} is, independently at each occurrence, H, =O, C_{1-4} alkyl, OR^a, CF_3, SR^a, F, CN, NO_2, NR^7R^8, -$C(O)NR^7R^8$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_pR^c$, -$C(O)R^a$, -$C(O)OR^a$, -$S(O)_pR^c$, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-,

$-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^d;

R^{11b} is, independently at each occurrence, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy-, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 R8;

R^{12} is, independently at each occurrence, H, F, or C_{1-4} alkyl;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, $-(CH_2)_n$-phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), $-C(O)R^c$, $-C(O)OR^c$, $-CONR^8R^c$, $-OCONR^8R^c$, $-S(O)_2R^c$, $-C(O)O-(C_{1-4}$ alkyl$)-OC(O)-(C_{1-4}$ alkyl), or $-C(O)O-(C_{1-4}$ alkyl$)-OC(O)-(C_{6-10}$ aryl); wherein the said alkyl, phenyl, heteroaryl, aryl are optionally substituted with 0-2 R^f;

R^{14} and R^{15} are, independently at each occurrence, H, F, or C_{1-4} alkyl;

alternately, R^{14} combines with R^{15} to form =O;

R^a is, independently at each occurrence, H, CF_3, C_{1-6} alkyl, $-(CH_2)_r-C_{3-7}$ cycloalkyl, $-(CH_2)_r-C_{6-10}$ aryl, or $-(CH_2)_r$-5- to 10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; wherein said cycloalkyl, aryl and heteroaryl groups are optionally substituted with 0-2 R^f;

R^b is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl,

-$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or -$(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d;

R^c is, independently at each occurrence, CF_3, C_{1-6} alkyl substituted with 0-2 R^f, C_{3-6} cycloalkyl substituted with 0-2 R^f, C_{6-10} aryl, 5- to 10-membered heteroaryl, (C_{6-10} aryl)-C_{1-4} alkyl, or (5- to 10-membered heteroaryl)-C_{1-4} alkyl, wherein said aryl and heteroaryl groups are optionally substituted with 0-3 R^f;

R^d is, independently at each occurrence, H, =O, =NR^8, OR^a, F, Cl, Br, I, CN, NO_2, -NR^7R^8, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -$NR^8C(O)R^a$, -$C(O)NR^7R^8$, -$SO_2NR^8R^9$, -$NR^8SO_2NR^8R^9$, -NR^8SO_2-C_{1-4} alkyl, -$NR^8SO_2CF_3$, -NR^8SO_2-phenyl, -$S(O)_2CF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, -$(CF_2)_rCF_3$, C_{1-6} alkyl substituted with 0-2 R^e, C_{2-6} alkenyl substituted with 0-2 R^e, or C_{2-6} alkynyl substituted with 0-2 R^e;

R^e is, independently at each occurrence, =O, OR^a, F, Cl, Br, I, CN, NO_2, -NR^8R^9, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)R^a$, -$NR^8C(O)R^a$, -$C(O)NR^7R^8$, -$SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, -NR^8SO_2-C_{1-4} alkyl, -$NR^8SO_2CF_3$, -NR^8SO_2-phenyl, -$S(O)_2CF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, or -$(CF_2)_rCF_3$;

R^f is, independently at each occurrence, H, =O, -$(CH_2)_r$-OR^g, F, Cl, Br, I, CN, NO_2, -$NR^{9a}R^{9a}$, -$C(O)R^g$, -$C(O)OR^g$, -$NR^{9a}C(O)R^g$, -$C(O)NR^{9a}R^{9a}$, -$SO_2NR^{9a}R^{9a}$, -$NR^{9a}SO_2NR^{9a}R^{9a}$, -$NR^{9a}SO_2$-C_{1-4} alkyl, -$NR^{9a}SO_2CF_3$, -$NR^{9a}SO_2$-phenyl, -$S(O)_2CF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, -$(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or -$(CH_2)_n$-phenyl;

R^g is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl;

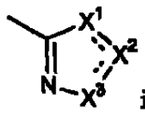
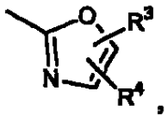
n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

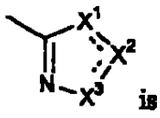
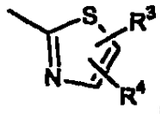
s, at each occurrence, is selected from 1, 2, 3, and 4;

provided that:

(a). when group  is  ,

i. and when L is –NHC(O)-, R^{14} does not combine with R^{15} to form =O;

ii. and when L is –C(O)NH- and A is phenyl, R^1 is not –NHC(O)H;

(b). when group  is  ,

i. and when L is –NHC(O)- and R^3 combines with R^4 to form a phenyl ring fused with the thiazole, the phenyl ring is substituted with at least one R^{3a};

ii. and when L is –C(O)NH- and A is phenyl, R^1 is not –NHC(O)H; and

(c). A is not a substituted or unsubstituted oxazolinone, thiophene, oxadiazole, or furan.

19. A compound according to Claim 18, wherein:

A is C_{3-8} cycloalkyl substituted with 0-1 R^1 and 0-3 R^2, C_{4-8} cycloalkenyl substituted with 0-1 R^1 and 0-3 R^2, phenyl substituted with 0-1 R^1 and 0-3 R^2, naphthyl substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2; provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

Z is $-C(R^{11})(R^{12})-$;

L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, or $-NR^{10}C(O)CH_2-$;

R^3 is, independently at each occurrence, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-C_{3-8} cycloalkyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and

R^{3d}, -$(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, -$(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or -$(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

R^4 is H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, -$C(O)R^a$, -$C(O)OR^a$, -NR^7R^8, -$C(O)NR^8R^9$, -$NR^7C(O)R^b$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_pR^c$, -$S(O)R^c$, -$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{4b};

R^6 is, independently at each occurrence, H, C_{1-6} alkyl, -CH_2OR^a, -$C(O)R^c$, -$C(O)_2R^c$, or -$(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, -$(CH_2)_r$-phenyl substituted with 0-3 R^d, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d; and

R^{11} is C_{1-4} haloalkyl, -$(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or -$(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

20. A compound according to Claim 18, wherein:

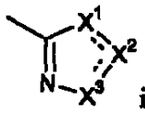
A is C_{5-6} cycloalkyl substituted with 0-1 R^1 and 0-2 R^2, C_{5-6} cycloalkenyl substituted with 0-1 R^1 and 0-2 R^2,, phenyl substituted with 0-1 R^1 and 0-3 R^2, naphthyl substituted with 0-1 R^1 and 0-3 R^2, or a 5- to 10-membered heterocycle

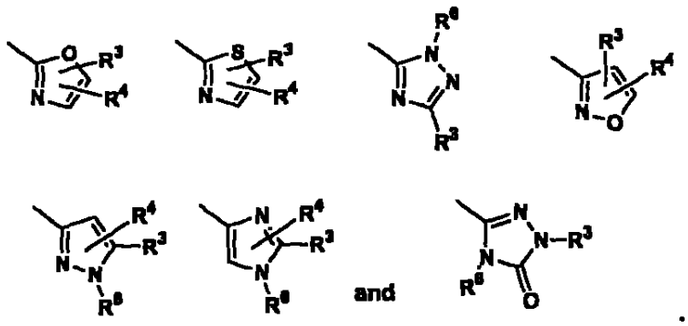
comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-1 R^1 and 0-3 R^2; provided when A is a heterocycle containing one or more nitrogen atoms, A is not attached to L via any of the nitrogen atoms on the A ring;

R^3 is, independently at each occurrence, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d}; and

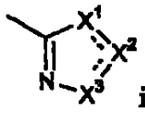
R^6 is, independently at each occurrence, H or C_{1-6} alkyl.

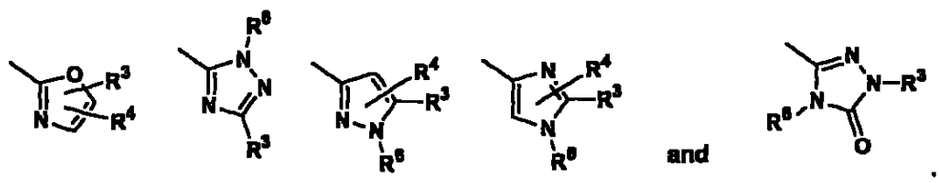
21. A compound according to Claim 18, wherein:

the group  is selected from:



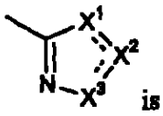
22. A compound according to Claim 18, wherein:

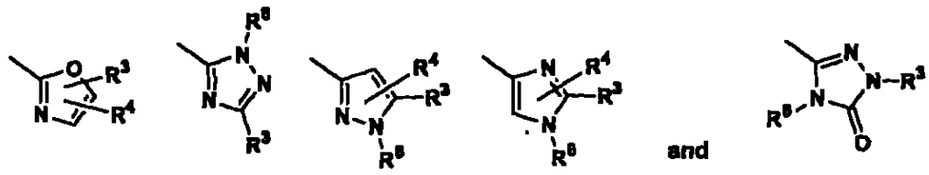
the group  is selected from:



23. A compound according to Claim 18, wherein:

A is substituted with 0-1 R^1 and 0-2 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

the group  is selected from:



;

Z is $-CH(R^{12})-$;

L is $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, or $-NR^{10}C(O)CH_2-$;

R^3 is, independently at each occurrence, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-indanyl substituted with 0-3 R^{3a} and 0-1 R^{3d} or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^{3a} and 0-1 R^{3d};

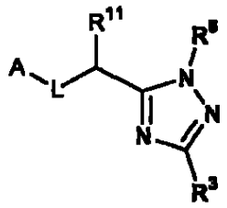
R^4 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^{4a}, C_{2-6} alkenyl substituted with 0-2 R^{4a}, C_{2-6} alkynyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^{4b};

R^6 is H, C_{1-6} alkyl, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{10a}, $-(CH_2)_r$-phenyl substituted with 0-2 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^d; and

R^{12} is, independently at each occurrence, H, *F*, or Me.

24. A compound according to Claim 18, wherein the compound is of Formula (VI):



(VI)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, within the scope of the eighteenth aspect wherein:

R^3 is $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_sC(O)NR^8(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-phenyl substituted with 0-3 R^{3a} and 0-1 R^{3d}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{3a}, $-(CH_2)_r$-indanyl substituted with 0-2 R^{3a}, or $-(CH_2)_r$-5-10 membered heterocycle comprising: carbon atoms and 1-4

heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{3a} and 0-1 R^{3d};

R^6 is, independently at each occurrence, H, C_{1-6} alkyl, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, or $-(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^{10} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-3 R^{10a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^d, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^d; and

R^{11} is C_{1-4} haloalkyl, $-(CH_2)_rC(O)NR^8R^9$, C_{1-6} alkyl substituted with 0-3 R^{11a}, C_{2-6} alkenyl substituted with 0-3 R^{11a}, C_{2-6} alkynyl substituted with 0-3 R^{11a}, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^{11b}.

25. A compound according to Claim 24, wherein:

R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, $-NHEt$, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

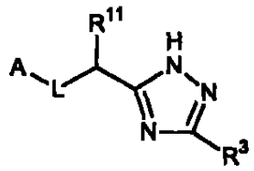
R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)_r$-phenyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, naphthyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, indanyl substituted with 0-2 R^{3a} and 0-1 R^{3d}, or a $-(CH_2)_r$-5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a} and 0-1 R^{3d};

R^6 is H;

R^{10} is, independently at each occurrence, H, Me, benzyl, phenethyl, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, or $-CH_2CH_2CONHCH_2CH_2Ph$; and

R^{11} is C_{1-6} alkyl, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r-C_{3-7}$ cycloalkyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, $-(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or $-(CH_2)_r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{11b}.

26. A compound according to Claim 18, wherein the compound is of Formula (VII):



(VII)

or its stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof,

A is substituted with 0-2 R^1 and 0-1 R^2 and selected from: C_{3-7} cycloalkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, indazolyl, benzimidazolyl, benzisoxazolyl, isoquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinazolinyl, 1H-quinazolin-4-onyl, 2H-isoquinolin-1-onyl, 3H-quinazolin-4-onyl, 3,4-dihydro-2H-isoquinolin-1-onyl, 2,3-dihydroisoindolinonyl, and phthalazinyl;

L is -C(O)NH- or -NHC(O)-;

R^1 is, independently at each occurrence, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-Bu})$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t\text{-Bu})$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, or $-CH_2R^{1a}$;

R^3 is $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$,

-C(O)NH_2, -C(O)NHMe, -C(O)NHBn, phenyl substituted with 0-2 R^{3a}, naphthyl substituted with 0-2 R^{3a}, indanyl substituted with 0-2 R^{3a}, or a 5-to 10-membered heterocycle comprising: carbon atoms and 1-2 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{3a};

R^4 is H, F, Cl, Br, CF_3, CO_2H, CO_2Me, CO_2Et, C_{1-6} alkyl substituted with 0-2 R^{4a}, phenyl substituted with 0-2 R^{4b}, or 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{4b};

R^{11} is C_{1-6} alkyl, -$CH_2CONR^8R^9$, -$CH_2CH_2CONR^8R^9$, -CH_2OBn, -CH_2SBn, -$(CH_2)_r$-C_{3-7} cycloalkyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-phenyl substituted with 0-2 R^{11b}, -$(CH_2)_r$-naphthyl substituted with 0-2 R^{11b}, or -$(CH_2)_r$-5- to 10-membered heteroaryl substituted with 0-2 R^{11b} and selected from thiazolyl, oxazolyl, triazolyl, tetrazolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl; and

R^{11b} is, independently at each occurrence, H, F, Cl, Br, CF_3, OMe, OEt, O(*i*-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, -NH_2, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)NR^7R^8$, -$NR^7C(O)R^b$, -$NR^8C(O)_2R^c$, -$S(O)_pNR^8R^9$, -$NR^8S(O)_pR^c$, -SO_2R^c, C_1-C_4-alkyl, Ph, or Bn;

alternately, when two R^{11b} groups are substituents on adjacent atoms they may be taken together with the atoms to which they are attached to form a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ and substituted with 0-2 Rg.

27. A compound according to Claim 26, wherein:

A is 4-CH_2NH_2-cyclohexyl or 4-amidino-phenyl; and

R^3 is phenyl, 3-CN-phenyl, 4-CN-phenyl, 3-Br-phenyl, 4-Br-phenyl, 3-OMe-phenyl, 4-OMe-phenyl, 3-CF_3-phenyl, 4-CF_3-phenyl, 3-CO_2H-phenyl,

4-CO_2H-phenyl, 4-CO_2Me-phenyl, 4-CH_2CO_2H-phenyl, 4-CH_2CO_2Me-phenyl, 3-$CONH_2$-phenyl, 4-$CONH_2$-phenyl, 4-CONHMe-phenyl, 4-$CON(Me)_2$-phenyl, 4-CH_2CONH_2-phenyl, 4-amidino-phenyl, or 2,4-diF-phenyl.

28. A compound selected from:

(*S*)-4-carbamimidoyl-N-(2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)benzamide,

(*S*)-4-(aminomethyl)-N-(2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethyl)-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-{1-[4-(4-cyano-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-{1-[4-(4-bromo-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-{1-[4-(4-methoxy-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[2-(1-benzyl-1*H*-imidazol-4-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-*trans*-cyclohexanecarboxamide,

(S)-3-(2-{1-[*trans*-(4-Aminomethyl)-cyclohexanecarboxamido]-2-phenyl-ethyl}-1*H*-imidazol-4-yl)-benzoic acid methyl ester,

(S)-4-(aminomethyl)-N-{1-[4-(3-fluoro-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-{1-[4-(3-bromo-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(*S*)-4-(aminomethyl)-N-[2-(3-chlorophenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(*S*)-4-(aminomethyl)-N-[2-(4-chlorophenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(*S*)-4-(aminomethyl)-N-[1-(4-phenyl-1H-imidazol-2-yl)-2-(2-pyridyl)ethyl]-*trans*-cyclohexanecarboxamide,

(*S*)-4-(aminomethyl)-N-[2-phenyl-1-(4-thiazol-2-yl-1*H*-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(*S*)-4-(aminomethyl)-N-[2-phenyl-1-(4-pyridin-2-yl-1*H*-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-[4-(2-{1-[*trans*-(4-aminomethyl)-cyclohexanecarboxamido]-2-phenyl-ethyl}-1*H*-imidazol-4-yl)-phenyl]-acetic acid,

(*S*)-4-(aminomethyl)-N-{1-[(4-carbamoylmethyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(S)-[4-(2-{1-[(4-aminomethyl)-cyclohexanecarboxamido]-2-phenyl-ethyl}-1*H*-imidazol-4-yl)]-benzamide,

(S)-[3-(2-{1-[(4-aminomethyl)-cyclohexanecarboxamido]-2-phenyl-ethyl}-1*H*-imidazol-4-yl)]-benzamide,

(S)-4-(2-(1-*trans*-(4-aminomethyl)-cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)-N,N-dimethylbenzamide,

(S)-2-(1-*trans*-(4-aminomethyl)-cyclohexanecarboxamido)-2-phenylethyl)-1H-benzo[d]imidazole-5-carboxamide,

N-(4-carbamimidoylphenyl)-3-phenyl-2-(4-phenyl-1H-imidazol-2-yl)propanamide,

4-(2-(1-(4-carbamimidoylphenylamino)-1-oxo-3-phenylpropan-2-yl)-1H-imidazol-4-yl)benzamide,

4-(2-(1-(1-aminoisoquinolin-6-ylamino)-1-oxo-3-phenylpropan-2-yl)-1H-imidazol-4-yl)benzamide,

4-(2-(4-(4-carbamimidoylphenyl)-1H-imidazol-2-yl)-3-phenylpropanamido)benzamide,

(S)-4-(aminomethyl)-N-{1-[4-(2,4-difluoro-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-{1-[4-(4-fluoro-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

(S)-3-(2-(1-*trans*-(4-aminomethyl)-cyclohexanecarboxamido)-2-phenylethyl)-1H-imidazol-4-yl)-benzoic acid,

(S)-N-(1-(4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl)-2-phenylethyl)-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

4-[2-[1-[4-[4-(carbamimidoylphenyl]-1H-imidazol-2-yl]-2-phenylethyl]-1H-imidazol-4-yl]-benzamide,

(S)-4-(aminomethyl)-N-[1-(4-phenyl-1H-imidazol-2-yl)-2-(4-pyridinyl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]amino]-2-phenylethyl]-4-(bromo-1H-imidazol-5-yl)-benzamide,

(S)-3-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-1H-imidazol-4-yl]- phenylacetic acid,

(S)-3-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-1H-imidazol-4-yl]- phenylacetamide,

(S)-4-(aminomethyl)-N-[1-[4-(3-hydroxyphenyl)-1H-imidazol-2-yl]-2-phenylethyl]-*trans*-cyclohexanecarboxamide,

(S)-3-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-1H-imidazol-4-yl]-phenylacetic acid, ethyl ester,

2-[4-(4-Carbamimidoyl-phenyl)-1*H*-imidazol-2-yl]-3,*N*-diphenyl-propionamide,

(S)-4-(aminomethyl)-N-[2-(4-fluorophenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[2-[4-(benzyloxy)phenyl]-1-(4-phenyl-1H-imidazol-2-yl) ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[2-(4-benzoylphenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[1-(4-phenyl-1H-imidazol-2-yl)-2-[3-(trifluoromethyl)phenyl]ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[-2-(3-nitrophenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[2-(2-chlorophenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[2-(1-naphthalenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[2-(2-naphthalenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[-1-[4,5-bis(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-phenylethyl]-*trans*-cyclohexanecarboxamide,

(S)-4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-4-(trifluoromethyl)-1H-imidazol-5-yl]-benzamide,

(S)-N-[1-[4-[4-(carbamimidoyl)phenyl]-1H-imidazol-2-yl]-2-phenylethyl]-benzamide,

(S)-4-(aminomethyl)-N-[2-(2-bromophenyl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-bromo-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)—*trans*-cyclohexanecarboxamide,

(S)-5-[4-(carbamoylphenyl]-2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-1H-imidazole-4-carboxylic acid, methyl ester,

4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-[2-(trifluoromethoxy)phenyl]ethyl]-1H-imidazol-4-yl]-benzamide,

4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-[2-(difluoromethoxy)phenyl]ethyl]-1H-imidazol-4-yl]-benzamide,

(S)-N-[1-[4-[4-(carbamoyl)phenyl]-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)- benzamide,

(S)-N-[1-[4-[4-(carbamoyl)phenyl]-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-2-fluoro- benzamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-benzamide,

(S)-3-amino-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]- 1H-indazole-6-carboxamide,

(S)-3-amino-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-1,2-benzisoxazole-6-carboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-2-fluoro-benzamide,

(S)-N-[1-[4-[4-(carbamimidoyl)phenyl]-1-(2-phenylethyl)-1H-imidazol-2-yl]-2-phenylethyl]- benzamide,

(S)-N-[1-[4-[4-(carbamimidoyll)phenyl]-1-methyl-1H-imidazol-2-yl]-2-phenylethyl]-benzamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-2-fluoro-5-methoxy-benzamide,

(S)-4-[2-[(1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-4-chloro-1H-imidazol-5-yl]-benzamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-1,4-benzenedicarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(2,2-dimethyl-1,3-benzodioxol-4-yl)ethyl]-4-(aminomethyl)--*trans*-cyclohexanecarboxamide,

4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-[3-(difluoromethoxy)phenyl]ethyl]-1H-imidazol-4-yl]-benzamide,

(S)-4-[2-[1-[4-(aminomethyl)cyclohexanecarboxamido]-2-phenylethyl]-4-phenyl-1H-imidazol-5-yl]-benzamide,

(S)-1-amino-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-6-isoquinolinecarboxamide,

(S)-1-amino-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-5,6,7,8-tetrahydro-6-isoquinolinecarboxamide,

N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(3-phenoxyphenyl)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(2-phenoxyphenyl)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

1-amino-N-[(1S)-1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-5,6,7,8-tetrahydro-(6S)- 6-isoquinolinecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(2-nitrophenyl)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[-1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(3-nitrophenyl)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(2-aminophenyl)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(3-aminophenyl)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[1,1'-biphenyl]-2-ylethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[1,1'-biphenyl]-3-ylethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[3-[(phenylsulfonyl)amino]phenyl]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

N-[2-(2S)-[2-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[[*trans*-[4-(aminomethyl)cyclohexanecarboxamido]ethyl]phenyl]-phenylacetamide,

N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[(2S)-2-methyl-2-(2-phenylethyl)-1,3-benzodioxol-4-yl]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[(2R)-2-methyl-2-(2-phenylethyl)-1,3-benzodioxol-4-yl]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-4-(aminomethyl)-N-[1-[4-(4-amino-7-quinazolinyl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-*trans*-cyclohexanecarboxamide,

N-[2-[(2S)-2-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[[[*trans*-4-(aminomethyl)cyclohexancarboxamido]ethyl]phenyl]-benzenepropanamide,

(S)-N-1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[2-[(phenylsulfonyl)amino]phenyl]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[2-(phenylmethoxy)phenyl]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

N-[2-[(2S)-2-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[[[*trans*-4-(aminomethyl)cyclohexanecarboxamdno]ethyl]phenyl]-benzamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(2-bromophenyl)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-3,3-dimethylbutyl]-4-(aminomethyl)-, *trans*-cyclohexanecarboxamide,

(R)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-(phenylmethoxy)ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(R)-N-[1-[4-(3-amino-1H-indazol-6-yl)-1H-imidazol-2-yl]-2-[(phenylmethyl)thio]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-4-fluoro-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-N-[1-[4-(3-amino-5-fluoro-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

3-[2-[4-[4-(aminocarbonyl)phenyl]-1H-imidazol-2-yl]-2-[[[*trans*-4-(aminomethyl)cyclohexanecarboxamido]ethyl]-benzoic acid, methyl ester,

N-[1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-[3-(difluoromethoxy)phenyl]ethyl]-4-(aminomethyl)-*trans*-cyclohexanecarboxamide,

(S)-3-amino-N-[1-[4-[4-(carbamimidoyll)phenyl]-1H-imidazol-2-yl]-2-phenylethyl]-1H-indazole-5-carboxamide,

3-[2-[4-[4-(aminocarbonyl)phenyl]-1H-imidazol-2-yl]-2-[[[*trans*-4-(aminomethyl)cyclohexanecarboxamido]ethyl]-benzoic acid,

(S)- 3-Amino-N-{1-[4-(4-carbamimidoyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-1*H*-indazole-6-carboxamide,

(S)-N-{1-[4-(4-carbamimidoyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-1*H*-Indazole-6-carboxamide,

(S)-N-{1-[4-(4-carbamimidoyl-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-1*H*-Indole-6-carboxamide,

(S)-*N*-{1-[4-(4-carbamimidoyl-phenyl)-1-ethyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-benzamide,

N^1-{(S)-1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-2-fluoro-terephthalamide,

N^1-{(S)-1-[4-(4-amino-quinazolin-7-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-2-fluoro-terephthalamide,

1-amino-N-[(1S)-1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenylethyl]-5,6,7,8-tetrahydro-(6R)-6-isoquinolinecarboxamide,

(S)-1-amino-N-{1-[4-(4-amino-quinazolin-7-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-5,6,7,8-tetrahydro-isoquinoline-6-carboxamide,

(S)-1-amino-N-{1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}- 3-methyl-isoquinoline-6-carboxamide,

4-(2-{1-[(4-aminomethyl- *trans* -cyclohexanecarboamido]-2-[3-(piperidine-1-carbonyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(*o*-tolylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(methyl-phenyl-carbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(benzylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

(S)-N-{1-[4-(3-amino-7-fluoro-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-aminomethyl-*trans*-cyclohexanecarboxamide,

(S)-N-{1-[4-(3-amino-1*H*-indazol-5-yl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-aminomethyl-*trans*-cyclohexanecarboxamide,

(S)-N-{1-[4-(3-hydroxy-1*H*-indazol-5-yl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-aminomethyl-*trans*-cyclohexanecarboxamide,

(S) 4-aminomethyl-N-[1-(4-biphenyl-4-yl-1*H*-imidazol-2-yl)-2-phenyl-ethyl]-*trans*-cyclohexanocarboxamide,

(S)-4-aminomethyl-N-[1-(4-benzo[1,3]dioxol-5-yl-1*H*-imidazol-2-yl)-2-phenyl-ethyl]- cyclohexanecarboxamide,

(S)-4-aminomethyl-N-[1-(4-naphthalen-2-yl-1*H*-imidazol-2-yl)-2-phenyl-ethyl]-*trans*- cyclohexanecarboxamide,

N^4-{(S)-1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-2-methoxy-terephthalamide,

(S)-4-aminomethyl-N-{1-[4-(3-amino-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}- cyclohexanecarboxamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-isobutyl-carbamoyl-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(3-methyl-butylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-*tert*-butylcarbamoyl-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(4-chloro-benzylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(4-chloro-benzylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(4-methoxy-benzylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-phenethylcarbamoyl -phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-[2-(4-chloro-phenyl)-ethylcarbamoyl]-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-[2-(4-methoxy-phenyl)-ethylcarbamoyl]-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(3-phenyl-propylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(benzyl-methyl-carbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(methyl-phenethyl-carbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-*m*-tolyl-carbamoyl-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-*p*-tolyl-carbamoyl-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(4-fluoro-phenylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(naphthalene-1-ylcarbamoyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl- *trans*-cyclohexanecarboamido]-2-[3-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-phenyl]-ethyl}-1*H*-imidazol-4-yl)-benzamide,

(S)-N-[1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-(3-benzenesulfonylamino-phenyl)-ethyl]- 4-Aminomethyl-tran-cyclohexanecarboxamide,

(S)-N-{1-[4-(4-benzyloxy-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-aminomethyl-*trans*-cyclohexanecarboxamide,

(S)-N-{1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-1-Oxo-1,2-dihydro-isoquinoline-6-carboxamide,

(S)-N-{1-[5-chloro-4-(2,4-diamino-quinazolin-7-yl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-aminomethyl-*trans*-cyclohexanecarboamide,

(S)-N-{1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-3-amino-1*H*-indazole-5-carboxamide,

4-(2-{(S)-1-[(4-aminomethyl-*trans*-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-bromo-1*H*-imidazol-4-yl)-2-fluoro-benzamide,

4-(2-{(S)-1-[(4-aminomethyl-*trans*-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-chloro-1*H*-imidazol-4-yl)-2-fluoro-benzamide,

(S)-N-{1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-1-Oxo-1,2,3,4-tetrahydro-isoquinoline-6-carboxamide,

(S)-N-[1-(5-methyl-4-phenyl-1*H*-imidazol-2-yl)-2-phenyl-ethyl]- 4-aminomethyl-*trans*-cyclohexanecarboxamide,

4-(2-{(S)-1-[(4-aminomethyl-*trans*-cyclohexanecarbonyl)-amino]-2-phenyl-ethyl}-5-methyl-1*H*-imidazol-4-yl)-benzamide,

(S)-N-{1-[4-(3-amino-1*H*-indazol-6-yl)-5-methyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-aminomethyl-*trans*-cyclohexanecarboxamide,

1-amino-N-{(S)-1-[4-(4-carbamoyl-phenyl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-5,6,7,8-totrahydro-isoquinoline-6-carboxamide,

1-amino-N-{(S)-1-[4-(4-carbamoyl-phenyl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-5,6,7,8-tetrahydro-isoquinoline-6-carboxylic acid,

1-amino-N-{(S)-1-[4-(4-carbamoyl-phenyl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-5,6,7,8-tetrahydro-isoquinoline-6-carboxamide,

1-amino-N-{(S)-1-[4-(4-carbamoyl-phenyl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-5,6,7,8-tetrahydro-isoquinoline-6-carboxylic acid,

4-aminomethyl-N-{(S)-1-[4-(6-amino-pyridin-3-yl)-5-methyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

4-aminomethyl-N-{(S)-1-[4-(3-chloro-phenyl)-5-methyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

5-(2-{(S)-1-[(4-aminomethyl-cyclohexanecarboxamido]-2-phenyl-ethyl}-5-methyl-1*H*-imidazol-4-yl)-thiophene-2-carboxylic acid,

5-(2-{(S)-1-[(4-aminomethyl-cyclohexanecarboxamido]-2-phenyl-ethyl}-5-methyl-1*H*-imidazol-4-yl)-thiophene-2-carboxamide,

N^4-{(S)-1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-2-phenoxymethyl-terephthalamide,

N-{(S)-1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-aminomethyl-2-benzyl-benzamide,

6(S)-1-amino-N-{(S)-1-[5-chloro-4-(4-cyano-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-5,6,7,8-tetrahydro-isoquinoline-6-carboxamide,

6(R)-1-amino-N-{(S)-1-[5-chloro-4-(4-cyano-phenyl)-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-5,6,7,8-tetrahydro-isoquinoline-6-carboxamide,

N-{(S)-1-[4-(3-amino-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-4-methyl-benzamide,

4-(2-{(S)-2-(3-acetylamino-phenyl)-1-[(4-aminomethyl-cyclohexanecarboxamido]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-aminomethyl-N-{(S)-1-[5-(3-amino-1*H*-indazol-6-yl)-1*H*-imidazol-2-yl]-3-[(5-methyl-pyrazin-2-ylmethyl)-carbamoyl]-propyl}-cyclohexanecarboxamide,

4-aminomethyl-N-[(S)-1-[5-(3-amino-1*H*-indazol-6-yl)-1*H*-imidazol-2-yl]-3-(benzyl-methyl-carbamoyl)-propyl]- cyclohexanecarboxamide,

4-aminomethyl-N-[(S)-1-[5-(3-amino-1*H*-indazol-6-yl)-1*H*-imidazol-2-yl]-3-(benzyl-carbamoyl)-propyl]- cyclohexanecarboxamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(ethyl-methyl-carbamoyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(isopropyl-methyl-carbamoyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(isobutyl-methyl-carbamoyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(methyl-phenyl-carbamoyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(ethyl-phenyl-carbamoyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(methyl-*m*-toluyl-carbamoyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(methyl-*p*-toluyl-carbamoyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-[2-(1-[(4-aminomethyl-cyclohexanecarboxamido]-2-{3-[(3-chloro-benzyl)-methyl-carbamoyl]-phenyl}-ethyl)-5-chloro-1*H*-imidazol-4-yl]-benzamide,

4-[2-(1-[(4-aminomethyl-cyclohexanecarboxamido]-2-{3-[(4-chloro-benzyl)-methyl-carbamoyl]-phenyl}-ethyl)-5-chloro-1*H*-imidazol-4-yl]-benzamide,

4-[2-(1-[(4-aminomethyl-cyclohexanecarboxamido]-2-{3-[2-(2-chloro-phenyl)ethylcarbamoyl]-phenyl}-ethyl)-5-chloro-1*H*-imidazol-4-yl]-benzamide,

4-[2-(1-[(4-aminomethyl-cyclohexanecarboxamido]-2-{3-[2-(3-chloro-phenyl)ethylcarbamoyl]-phenyl}-ethyl)-5-chloro-1*H*-imidazol-4-yl]-benzamide,

4-[2-(1-[(4-aminomethyl-cyclohexanecarboxamido]-2-{3-[2-(4-chloro-phenyl)ethylcarbamoyl]-phenyl}-ethyl)-5-chloro-1*H*-imidazol-4-yl]-benzamide,

4-aminomethyl-*N*-{(S)-1-[4-(4-methanesulfonylamino-phenyl)-5-methyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

4-aminomethyl-*N*-[(S)-1-[5-(3-amino-1*H*-indazol-6-yl)-1*H*-imidazol-2-yl]-3-(cyclopropylmethyl-carbamoyl)-propyl]-*trans*-cyclohexanecarboxamide,

4-aminomethyl-*N*-[(S)-1-[5-(3-amino-1*H*-indazol-6-yl)-1*H*-imidazol-2-yl]-3-(2-(phenyl)ethyl-carbamoyl)-propyl]-*trans*-cyclohexanecarboxamide,

4-aminomethyl-*N*-{(S)-1-[4-(4-acetylamino-phenyl)-5-methyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

4-aminomethyl-*N*-{(S)-1-[4-(4-hydroxy-phenyl)-5-methyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

4-[2-(1-[(4-aminomethyl-cyclohexanecarboxamido]-2-{3-[methyl-(2-pyridin-2-yl-ethyl)-carbamoyl]-phenyl}-ethyl)-5-chloro-1*H*-imidazol-4-yl]-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(2,3-dihydro-indole-1-carbonyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(1,3-dihydro-isoindole-2-carbonyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(2,3-dihydro-1,4-benzoxazine-4-carbonyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-(2-{1-[(4-aminomethyl-cyclohexanecarboxamido]-2-[3-(6-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl)-phenyl]-ethyl}-5-chloro-1*H*-imidazol-4-yl)-benzamide,

4-aminomethyl-*N*- {(S)-1-[4-(1*H*-indazol-6-yl)-5-methyl-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-cyclohexanecarboxamide,

1-amino-*N*-{(S)-1-[4-(3-amino-7-fluoro-1*H*-indazol-6-yl)-5-chloro-1*H*-imidazol-2-yl]-2-phenyl-ethyl}-*trans*-5,6,7,8-tetrahydro-isoquinoline-6-carboxamide,

4-aminomethyl-N-{1-[4-(1H-indazol-6-yl)-5-methyl-1H-imidazol-2-yl]-2-phenyl-ethyl}-trans-cyclohexanecarboxamide,

4-aminomethyl-N-{1-[4-(3-acetylamino-phenyl)-5-methyl-1H-imidazol-2-yl]-2-phenyl-ethyl}-trans-cyclohexanecarboxamide,

5-(2-{1-[trans-4-aminomethyl-cyclohexanecarboxamido]-2-phenyl-ethyl}-5-chloro-1H-imidazol-4-yl)-thiophene-2-carboxylic acid,

N1-{1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenyl-ethyl}-2-chloro-terephthalamide,

4-aminomethyl-N-{1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-3-[(thiazol-2-ylmethyl)-carbamoyl]-propyl}-trans-cyclohexanecarboxamide,

4-aminomethyl-N-{1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-3-[(pyridin-2-ylmethyl)-carbamoyl]-propyl}-trans-cyclohexanecarboxamide,

4-aminomethyl-N-{1-[5-methyl-4-(3-oxo-2,3-dihydro-1H-isoindol-5-yl)-1H-imidazol-2-yl]-2-phenyl-ethyl}-trans-cyclohexanecarboxamide,

[4-(2-{1-[trans-4-aminomethyl-cyclohexanecarboxamido]-2-phenyl-ethyl}-5-methyl-1H-imidazol-4-yl)-phenyl]-carbamic acid methyl ester,

4-(2-{1-[trans-4-aminomethyl-cyclohexanecarboxamido]-2-[3-(methyl-phenyl-sulfamoyl)-phenyl]-ethyl}-5-chloro-1H-imidazol-4-yl)-benzamide,

4-{2-[1-[trans-4-aminomethyl-cyclohexanecarboxamido]-2-(3-benzenesulfonyl-methyl-amino-phenyl)-ethyl]-5-chloro-1H-imidazol-4-yl}-benzamide,

4-(2-{1-[trans-4-aminomethyl-cyclohexanecarboxamido]-2-[3-(benzoyl-methyl-amino)-phenyl]-ethyl}-5-chloro-1H-imidazol-4-yl)-benzamide,

4-aminomethyl-N-{1-[4-(1-imino-4-oxo-1,2,3,4-tetrahydro-phthalazin-6-yl)-5-methyl-1H-imidazol-2-yl]-2-phenyl-ethyl}-trans-cyclohexanecarboxamide,

4-aminomethyl-N-(1-{5-methyl-4-[3-(2H-tetrazol-5-yl)-phenyl]-1H-imidazol-2-yl}-2-phenyl-ethyl)-trans-cyclohexanecarboxamide,

N-{1-[4-(3-amino-1H-indazol-6-yl)-5-chloro-1H-imidazol-2-yl]-2-phenyl-ethyl}-2-fluoro-4-methyl-benzamide,

or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

29. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any one of Claims 1-28.

30. A method of treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of any one of Claims 1-28.

31. A method of treating a thromboembolic disorder according to Claims 30, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart.

32. A method according to Claim 31, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.

33. A compound of any one of Claims 1-28 for use in therapy.

34. · Use of a compound of any one of Claims 1-28 for the manufacture of a medicament for the treatment of a thromboembolic or an inflammatory disorder.

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

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(81) Estados Designados: *(a menos que se indique de otra forma, para cada clase de protección regional disponible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Estados Designados: *(a menos que se indique de otra forma, para cada clase de protección regional disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones bajo la Regla 4.17:

- *en cuanto al derecho del solicitante para solicitar y otorgar una patente (Regla 4.17(ii)) para los siguientes designaciones:* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, Patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Patente euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- *en cuanto al derecho del solicitante para reivindicar la prioridad de la solicitud más anticipada (Regla 4.17(iii)) para todas las designaciones*

Publicada

- *con el reporte de búsqueda internacional*

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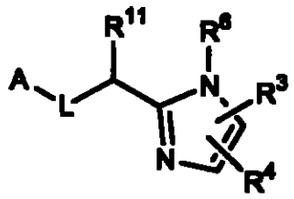
(54) Título: HETEROCICLOS DE CINCO MIEMBROS UTILES COMO INHIBIDORES DE LA SERINA PROTEASA

(57) Resumen: La presente invención proporciona un método para tratar un trastorno trombótico o inflamatorio administrando a un paciente que necesita del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la fórmula (I) o Fórmula (V): o un estereoisómero o una forma de sal o solvato farmacéuticamente aceptables del mismo, en donde las variables A, L, Z, R3, R4, R6, R11, X1, X2, y X3 son como se definen en la presente. Los compuestos de la Fórmula (I) son útiles como inhibidores selectivos de las enzimas de serina proteasa de la cascada de coagulación y/o sistema de activación por contacto; por ejemplo trombina, factor Xa, factor XIa, factor IXa, factor VIIa, y/o calicreína de plasma. En particular, se refiere a compuestos que son inhibidores selectivos del factor XIa. Esta invención también proporciona compuestos dentro del alcance de la Fórmula I y se refiere a composiciones farmacéuticas que comprenden estos compuestos.

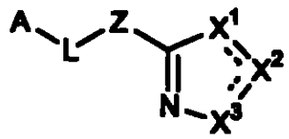
HETEROCICLOS DE CINCO MIEMBROS UTILES COMO INHIBIDORES DE LA SERINA PROTEASA

CAMPO DE LA INVENCIÓN

La presente invención proporciona un método para tratar un trastorno trombótico o inflamatorio administrando a un paciente que necesita del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la fórmula (I) o Fórmula (V):



(I)



(V)

o un estereoisómero o forma de sal o solvato farmacéuticamente aceptable del mismo, en donde las variables A, L, Z, R^3, R^4, R^6, R^{11}, X^1, X^2, y X^3 son como se definen en la presente. Los compuestos de la Fórmula (I) son útiles como inhibidores selectivos de las enzimas de serina proteasa de la cascada de coagulación y/o sistema de activación por contacto; por ejemplo trombina, factor Xa, factor XIa, factor IXa, factor VIIa, y/o calicreína de plasma. En particular, se refiere a compuestos que son inhibidores selectivos del factor XIa o inhibidores dobles de fXIa y la calicreína del plasma. Esta invención también se refiere a composiciones

farmacéuticas que comprenden estos compuestos y métodos de uso de los mismos.

ANTECEDENTES DE LA INVENCIÓN

El factor XIa es una serina proteasa de plasma involucrada en la regulación de la coagulación sanguínea. Aunque la coagulación sanguínea es una parte necesaria e importante de la regulación de la homeostasis del organismo, la coagulación sanguínea anormal también puede tener efectos perjudiciales. Por ejemplo, la trombosis es la formación o presencia de un coágulo sanguíneo dentro de un vaso sanguíneo o cavidad del corazón. Tal coágulo sanguíneo puede alojarse en un vaso sanguíneo bloqueando la circulación e induciendo un ataque cardiaco o apoplejía. Los trastornos tromboembólicos son la causa más grande de mortalidad y discapacidad en el mundo industrializado.

La coagulación sanguínea se inicia in vivo por el enlace de factor de tejido (TF) al factor VII(FVII) para generar el factor VIIa(FVIIa). El complejo TF:FVIIa resultante activa el factor IX(FIX) y el factor X(FX) lo que lleva a la producción del factor Xa(FXa). El FXa que se genera cataliza la transformación de protrombina en pequeñas cantidades de trombina antes de que esta trayectoria se caiga por el inhibidor de la trayectoria del factor de tejido (TFPI). El proceso de coagulación se propaga entonces además por medio

de la activación retroalimentada de los factores V, VIII y XI por cantidades catalíticas de trombina. (Walsh, P. N. Thromb. Haemostasis. 1999, 82, 234-242). El factor XIa juega un papel importante en la propagación en este circuito de amplificación y de esta manera es un objetivo atractivo para la terapia antitrombótica.

Una vía alternativa de inicio de la coagulación se opera cuando la sangre se expone a superficies artificiales (por ejemplo durante la hemodiálisis, cirugía cardiovascular "en bomba", injertos de vasos, sepsis bacterial). Este proceso también se llama activación de contacto. La absorción de superficie del factor XII lleva a un cambio conformacional en la molécula del factor XII, por ello facilitando la activación para las moléculas del factor XII proteolíticas activas (factor XIIa y factor XIIf). El factor XIIa (o XIIf) tiene un número de proteínas objetivo, incluyendo la precalicreína de plasma y el factor XI. La calicreína de plasma activa adicionalmente activa el factor XII, lo que lleva a una amplificación de la activación por contacto. La activación por contacto es un proceso mediado por la superficie que responde en parte a la regulación de trombosis e inflamación, y está mediada, al menos en parte, por las trayectorias humorales y celulares fibrinolíticas, de complemento, cininogeno/cinina, y otras (para revisión Coleman, R. Contac Activation Pathway, páginas 103-122 en

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Hemostasis and Trombosis, Lippincott Williams & Wilkins 2001; Schmaier A.H. Contact Activation, páginas 105-128 en Trombosis and Hemorrhage, 1998).

El factor XI es un cimógeno de una serina proteasa tipo tripsina y está presente en el plasma a una concentración relativamente baja. La activación proteolítica a un enlace R369-I370 interno proporciona una cadena pesada (369 aminoácidos) y una cadena ligera (238 aminoácidos). La última contiene una triada catalítica tipo tripsina típica (H413, D464, y S557). La activación del factor XI por trombina se considera que se presenta en superficies negativamente cargadas, más posiblemente en la superficie de plaquetas activadas. Las plaquetas que contienen sitios específicos de alta afinidad (0.8 nM) (130-500/plaqueta) para el factor XI activado. Después de la activación, el factor XIa se mantiene enlazado a la superficie y reconoce el factor IX como su substrato macromolecular normal (Galiani, D. Trends Cardiovasc. Med. 2000, 10, 198-204).

Además de los mecanismos de activación de retroalimentación descritos arriba, la trombina activa el inhibidor de fibrinolisis activado por trombina (TAFI), una carboxipeptidasa de plasma que desdobla la lisina de terminal C y los residuos de arginina en la fibrina, reduciendo la capacidad de la fibrina para aumentar el activador de plasminógeno de tipo de tejido (tPA)

dependiente de la activación de plasminógeno. En presencia de anticuerpos para FXIa, puede presentarse la lisis de coágulo más rápidamente en forma independiente de la concentración TAFI en el plasma. (Bouma, B. N. et al., Thromb. Res. 2001, 101, 329-354). De esta manera, los inhibidores del factor XIa se espera que sean anticoagulantes y profibrinolíticos.

La evidencia genética indica que el factor XI no se requiere para la homeostasis normal, lo que implica un perfil de seguridad superior del mecanismo del factor XI en comparación con los mecanismos antitrombóticos competentes. En contraste con la hemofilia A (deficiencia en el factor VIII) o hemofilia B (deficiencia en el factor IX), las mutaciones del gen del factor XI causan una deficiencia en el factor XI (hemofilia C) que resulta sólo en una diatesis de sangrado media a moderada caracterizada primariamente por una hemorragia post-operativa o post-traumática, pero raramente espontánea. El sangrado post-operativo se presenta mayormente en tejidos con altas concentraciones de actividad fibronolítica endógena (por ejemplo, cavidad oral y sistema urogenital). La mayoría de los casos se identifican fortuitamente por una prolongación preoperativa de APTT (sistema intrínseco) sin ninguna historia de sangrado previa.

La seguridad incrementada de la inhibición de XIa como

una terapia anticoagulación se soporta además por el hecho de que ratones agénicos con factor XI, que no tienen una proteína de factor XI detectable, experimentan un desarrollo normal, y tienen un intervalo de vida normal. No se ha notado evidencia de un sangrado espontáneo. El APTT (sistema intrínseco) se prolonga en una forma dependiente de la dosis de genes. Interesantemente, aún después de una estimulación severa del sistema de coagulación (transección de la cola), el tiempo de sangrado no se prolonga significativamente en comparación con las camadas paridas heterocigóticas y de tipo silvestre. (Gailiani, D. Frontiers in Bioscience 2001, 6, 201-207; Gailiani, D. et al. Blood Coagulation and Fibrinolysis 1997, 8, 134-144). Tomadas en conjunto, estas combinaciones sugieren que los altos niveles de inhibición del factor XIa deberían ser bien tolerados. Esto está en contraste con los experimentos de direccionamiento de genes con otros factores de coagulación.

La activación in vivo del factor XI puede determinarse por la formación de complejo con ya sea el inhibidor C1 o la antitripsina alfa 1. En un estudio de 50 pacientes con infarto al miocardio agudo (AMI), aproximadamente el 25% de los pacientes tuvo valores arriba del rango normal superior del complejo ELISA. Este estudio puede apreciarse como una evidencia de que al menos en una subpoblación de pacientes con AMI, la activación del factor XI contribuye a la

formación de trombina (Minnema, M.C. et al. Arterioscler. Thromb. Vasc. Biol. 2000, 20, 2489-2493). Un segundo estudio establece una correlación positiva entre la extensión de arteriosclerosis coronaria y el factor XIa en complejo con la antitripsina alfa 1 (Murakami, T. et al. Arterioscler Thromb Vasc Biol 1995, 15, 1107-1113). En otro estudio, los factores del nivel XI arriba del porcentaje 90 en pacientes se asociaron con un riesgo incrementado 2.2 veces para trombosis venosa (Meijers, J. C. M. et al. N. Engl. J. Med. 2000, 342, 696-701).

La calicreína de plasma es un cimógeno de una serina proteasa tipo tripsina, y está presente en el plasma de 35 hasta 50 µg/mL. La estructura del gen es similar a la del factor XI, general, la secuencia de aminoácido de la calicreína de plasma tiene 58% de homología del factor XI. La activación proteolítica por el factor XIIa a un enlace I 389-R390 interno proporciona una cadena pesada (371 aminoácidos) y una cadena ligera (248 aminoácidos). El sitio activo de la calicreína está contenido en la cadena ligera. La cadena ligera de la calicreína de plasma reacciona con inhibidores de proteasa incluyendo el inhibidor C1 y alfa 2 de macroglobulina. Interesantemente, la heparina acelera significativante la inhibición de la calicreína de plasma por la antitrombina III en presencia de cininógeno de alto peso molecular (HMWK). En la sangre, la mayoría de la calicreína

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de plasma circula en complejo con HMWK. La calicreína desdobla al HMWK para liberar la bradicinina. La bradicinina liberada resulta en un incremento de la permeabilidad vascular y la vasodilatación (para revisión, Coleman, R. Contact Activation Pathway, páginas 103-122 en Hemostasis and Thrombosis, Lippincott Williams & Wilkins 2001; Schmaier A. H. Contact Activation, páginas 105-128 en Thrombosis and Hemorrhage, 1998).

Las proteínas o péptidos que inhiben según se dice el factor XIa se describen en WO 01/27079. Hay ventajas al usar compuestos orgánicos pequeños, sin embargo, en la preparación de farmacéuticos, por ejemplo, compuestos pequeños generalmente tienen una mejor biodisponibilidad oral y compatibilidad en las formulaciones elaboradas para ayudar en la entrega del fármaco en comparación con proteínas o péptidos grandes. Los inhibidores de molécula pequeña del factor XIa se describen en la solicitud de patente EUA Publicada US20040235847A1 y publicación de solicitud de patente de EUA US20040220206A1.

Por otro lado, también es deseable hallar nuevos compuestos con características farmacológicas mejoradas en comparación con los inhibidores de serina proteasa conocidos. Por ejemplo, se prefiere encontrar nuevos compuestos que mejoren la actividad inhibidora del

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factor XIa y la selectividad para el factor XIa contra otras serinas proteasas. También, se prefiere hallar nuevos compuestos con una actividad inhibidora de la calicreína en plasma mejorada y una selectividad para la calicreína de plasma contra otras serina proteasas. También es deseable y preferible hallar compuestos con características ventajosas y mejoradas en una o más de las siguientes categorías, pero no limitadas a: (a) propiedades farmacéuticas; (b) requerimientos de dosis; (c) factores que reducen las características de concentración sanguínea máximo a mínimo; (d) factores que incrementan la concentración de fármaco activo en el receptor; (e) factores que reducen el riesgo para interacciones fármaco-fármaco clínicas; (f) factores que reducen el potencial para efectos colaterales adversos; y (g) factores que mejoran los costos de fabricación o factibilidad.

SUMARIO DE LA INVENCIÓN

La presente invención proporciona derivados novedosos de heterociclo de cinco miembros, y análogos de los mismos, que son útiles como inhibidores selectivos de las enzimas de serina proteasa, especialmente el factor XIa y/o la calicreína de plasma, o estereoisómeros o sales, solvatos o profármacos

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farmacéuticamente aceptables de los mismos.

La presente invención también proporciona procesos e intermediarios para hacer los compuestos de la presente invención o un estereoisómero o una forma de sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

La presente invención también proporciona composiciones farmacéuticas que comprenden un portador farmacéuticamente aceptable y una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la presente invención o una forma de sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

La presente invención también proporciona un método para la modulación de la cascada de coagulación y/o el sistema de activación por contacto que comprende administrar a un hospedador que necesita de tal tratamiento una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la presente invención o una forma de sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

La presente invención también proporciona un método para tratar trastornos tromboembólicos que comprende administrar a un hospedador que necesita de tal tratamiento una cantidad terapéuticamente efectiva de al

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menos uno de los compuestos de la presente invención o una forma de sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

La presente invención también proporciona un método para tratar trastornos de enfermedades inflamatorias que comprende administrar a un hospedador que necesita de tal tratamiento, una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la presente invención o una forma de sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

La invención también proporciona derivados novedosos de heterociclo de cinco miembros y análogos de los mismos, para usarse en la terapia.

La presente invención también proporciona el uso de los derivados de heterociclo de cinco miembros, y análogos de los mismos para la manufactura de un medicamento para el tratamiento de un trastorno tromboembólico.

La presente invención también proporciona el uso de los derivados heterociclos de cinco miembros, y análogos de los mismos para la manufactura de un medicamento para el tratamiento de un trastorno inflamatorio.

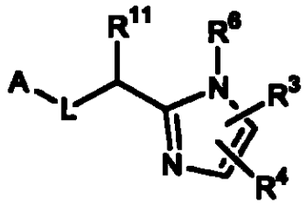
Estas y otras modalidades, que serán aparentes durante la siguiente descripción detallada, se han realizado por el descubrimiento de los inventores que

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los compuestos novedosos recientemente reivindicados de la presente invención, o formas de sal o profármacos farmacéuticamente aceptables de los mismos, son inhibidores del factor XIa efectivos y/o inhibidores de la calicreína de plasma.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

En un primer aspecto, la presente invención incluye, *inter alia*, un compuesto de la Fórmula (I):



(I)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos, en donde:

A es carbociclo C_{3-10} substituido con 0-1 R^1 y 0-3 R^2, o con un heterociclo de 5 hasta 12 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no está unido a L por medio de cualesquiera de los átomos de nitrógeno en el anillo A;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)_pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, o $-C(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-NH$(alquilo C_1-C_3), $-N$(alquilo C_1-$C_3)_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7CO_2R^a$, $-CH_2NH_2$, $-CH_2NH$(alquilo C_{1-3}), $-CH_2N$(alquilo $C_{1-3})_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH$(alquilo C_1-C_3), $-CH_2CH_2N$(alquilo $C_{1-3})_2$, $-CH$(alquilo C_{1-4})NH_2, $-C$(alquilo $C_{1-4})_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-ciclopropilo, o alquilo C_{1-6} substituido con 0-1 R^{1a};

R^{1a} es H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^2 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} substituido con 0-2 R^{2a}, alquenilo C_{2-6} substituido con 0-2 R^{2a}, alquinilo C_{2-6} substituido con 0-2 R^{2a}, $-(CH_2)_r$carbociclo C_{3-10} substituido con 0-3 R^{2b}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que

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comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{2b};

R^{2a} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{2b} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^C$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4}-;

alternativamente, cuando los grupos R^1 y R^2 son substituidos en átomos de anillo adyacente, estos pueden tomarse junto con los átomos en el anillo al cual se enlazan para formar un carbociclo o heterociclo de 5 a 7 miembros que comprende: átomos de carbono y 0-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el carbociclo o heterociclo está substituido con 0-2 R^{2b};

R^3 es $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$- heterociclo de 5- a 10- miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido

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con 0-3 R^{3a} y 0-1 R^{3d};

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, -C(O)-alquilo C_{1-4}, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, haloalquilo C_{1-4}, haloalcoxi C_{1-4}-, alquilo C_{1-6} substituido por R^{3d}, alquenilo C_{2-6} substituido por R^{3d}, alquinilo C_{2-6} substituido por R^{3d}, cicloalquilo C_{3-6} substituido por 0-1 R^{3d}, $-(CH_2)_r$- carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$-heterociclo de 5- hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3d};

alternativamente, cuando dos grupos R^{3a} se localizan en átomos adyacentes, estos pueden tomarse junto con los átomos a los cuales están enlazados para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3d};

R^{3b} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido

con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3c} es, independientemente cada que se presenta, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3d};

R^{3d} es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-S(O)_pR^C$, $-(CF_2)_rCF_3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, alquinilo C_{2-6} substituido con 0-2 R^e, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6}

substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^{4b}, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{4a} es, independientemente cada que se presenta, H, F, =O, alquilo C_{1-6}, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{4b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^C$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4}-;

alternativamente, los grupos R^3 y R^4 cuando se localizan en átomos adyacentes, pueden tomarse juntos para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3d};

R^6 es H;

R^7 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n-$ carbociclo C_{3-10}, $-(CH_2)_n-$(heteroarilo de 5-10 miembros), $-C(O)R^C$, -CHO, $-C(O)_2R^C$, $-S(O)_2R^C$, $-CONR^8R^C$, -

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$OCONHR^c$, $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(arilo C_{6-10}); en donde los alquilo, carbociclo, heteroarilo, y arilo están substituidos opcionalmente con 0-2 R^f;

R^8 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo, o $-(CH_2)_n-$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los alquilo, fenilo y heterociclo están substituidos opcionalmente con 0-2 R^f;

alternativamente, R^7 y R^8, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^d;

R^{8a} es, independientemente cada que se presenta, H, OH, alquilo C_{1-6}, alcoxi C_{1-4}, (arilo C_{6-10})-alcoxi C_{1-4}, $-(CH_2)_n-$fenilo, $-(CH_2)_n-$(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(arilo C_{6-10}); en donde el fenilo, arilo, y heteroarilo están opcionalmente substituidos con 0-2 R^f;

R^9 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo; en donde el alquilo y fenilo están substituidos opcionalmente con 0-2 R^f;

R^{9a} es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

alternativamente, R^8 y R^9, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, alquenilo C_{2-6} substituido con 0-3 R^{10a}, alquinilo C_{2-6} substituido con 0-3 R^{10a}, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

R^{10a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C-$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CR^{14}R^{15})_r-$ carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CR^{14}R^{15})_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{11b};

R^{11a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, CF_3, SR^a, F, CN, NO_2, $-NR^7R^8$, $-C(O)NR^7R^8$, -

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$NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^C$, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}-, $-(CH_2)_r$- carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^d;

R^{11b} es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^C$, $-SO_2R^C$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^C$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, $-(CH_2)r$- carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)r$- heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales están enlazados para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g;

R^{14} y R^{15} son, independientemente cada que se presentan, H, F, o alquilo C_{1-4};

alternativamente, R^{14} se combina con R^{15} para formar =O;

R^a es, independientemente cada que se presenta, H, CF_3,

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alquilo C_{1-6}, $-(CH_2)_r-$ cicloalquilo C_{3-7}, $-(CH_2)_r-$ arilo C_{6-10}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los grupos cicloalquilo, arilo y heterociclo son opcionalmente substituidos con 0-2 R^f;

R^b es, independientemente cada que se presenta, CF_3, OH, alcoxi C_{1-4}, alquilo C_{1-6} $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^c es, independientemente cada que se presenta, CF_3, alquilo C_{1-6} substituido con 0-2 R^f, cicloalquilo C_{3-6} substituido con 0-2 R^f, arilo C_{6-10}, heteroarilo de 5 hasta 10 miembros, (arilo C_{6-10})-alquilo C_{1-4}, o (heteroarilo de 5 hasta 10 miembros) alquilo C_{1-4}, en donde los grupos arilo y heteroarilo son opcionalmente substituidos con 0-3 R^f;

R^d es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2-$alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2-$fenilo, $-S(O)_2CF_3$, $-S(O)_p-$alquilo C_{1-4}, $-S(O)p-$fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, o alquinilo C_{2-6} substituido con 0-2 R^e;

R^e es, independientemente cada que se presenta, =O, OR^a,

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F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)p$- alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^f es, independientemente cada que se presenta, H, =O, $-(CH_2)_r-OR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-alquilo C_{1-4}, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, o $-(CH_2)_n$-fenilo;

R^g es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

n, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4;

p, cada que se presenta, se selecciona de 0, 1, y 2;

r, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4; y

s, cada que se presenta, se selecciona de 1, 2, 3, y 4;

con la condición de que:

(a). cuando L es $-C(O)NH-$, R^3 no es 2,4-diclorofenilo, 4-nitrofenilo o pentafluorofenilo;

(b). cuando L es $-C(O)NH-$, R^{11} no es $-CH_2$-(3-indolilo), $-(CH_2)_4NHCO_2(t\text{-}Bu)$ o $-(CH_2)_4NH_2$.

En un segundo aspecto, la presente invención incluye compuestos de la Fórmula (I), dentro del alcance del primer

aspecto en donde:

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2CONR^{10}-$, o $-NR^{10}COCH_2-$;

R^3 es $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_r-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{11a}, alquenilo C_{2-6} con 0-2 R^{11a}, alquinilo

C_{2-6} substituido con 0-2 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b}.

En un tercer aspecto, la presente invención incluye compuestos de la fórmula (I), dentro del alcance del primer aspecto en donde:

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, -NHEt, $-NHCO_2(t\text{-}Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a o $-CH_2R^{1a}$;

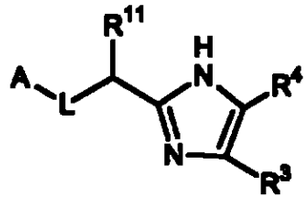
R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)$r-fenilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, naftilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, indanilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$- heterociclo 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, CF_3, OMe, NH_2, CO_2H, CO_2Me, CO_2Et, $-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{10} es, independientemente cada que se presenta, H, Me, bencilo, fenetilo, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, o $-CH_2CH_2CONHCH_2CH_2Ph$; y

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{11b}.

En un cuarto aspecto, la presente invención incluye un compuesto de la Fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos, dentro del alcance del primer aspecto en donde:

A está substituido con 0-1 R^1 y 0-2 R^2 y se selecciona de: cicloalquilo C_{3-7}, fenilo naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo,

quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

L es $-C(O)NH-$ o $-NHC(O)-$;

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-CMe_2NH_2$, $-NHEt$, $-NHCO_2(t\text{-}Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, fenilo substituido con 0-2 R^{3a}, naftilo substituido con 0-2 R^{3a}, indanilo substituido con 0-2 R^{3a}, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-2 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3a};

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{4b};

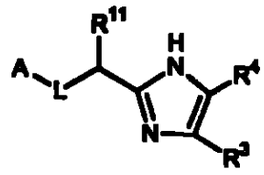
R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$ heteroarilo de 5 hasta 10 miembros substituidos con 0-2 R^{11b} y seleccionados

de tiazolilo, oxazolilo, triazolilo, tetrazolilo, imidazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, benzimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, tetrahidroquinolinilo, y tetrahidroisoquinolinilo; y

R^{11b} es, independientemente cada que se presenta, H, F, Cl, Br, CF_3, OMe, OEt, O(i-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, alquilo C_1-C_4-, Ph, o Bn;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos al cual están enlazados para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g.

En un quinto aspecto, la presente invención incluye un compuesto de la fórmula (II):

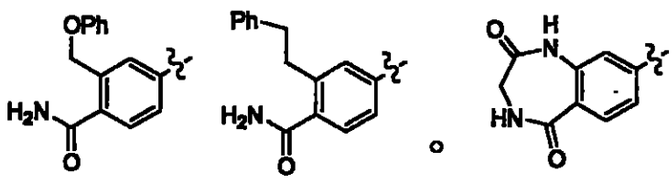


(II)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables del mismo, dentro

del alcance del primer aspecto en donde:

A es 4-CH_2NH_2-ciclohexilo, 4-CO_2Me-ciclohexilo, 4-$CONH_2$-ciclohexilo, 4-$NHCO_2$(t-Bu)-ciclohexilo, 4-$NHCO_2Bn$-ciclohexilo, fenilo, 4-Me-fenilo, 3-OMe-fenilo, 4-CH_2NH_2-fenilo, 3-$CONH_2$-fenilo, 4-$CONH_2$-fenilo, 3-amidino-fenilo, 4-amidino-fenilo, 2-F-4-Me-fenilo, 2-Bn-4-CH_2NH_2-fenilo, 4-SO_2NH_2-fenilo, 2-F-5-OMe-fenilo, 2-F-4-Cl-fenilo, 2-F-4-CH_2NH_2-fenilo, 2-F-4-$CONH_2$-fenilo, 2-Cl-4-$CONH_2$-fenilo, 2-Et-4-CH_2NH_2-fenilo, 2-NHEt-4-CH_2NH_2-fenilo, 2-OMe-4-$CONH_2$-fenilo, 3-OMe-4-$CONH_2$-fenilo, 1,2,3,4-tetrahidronaft-2-ilo, 3-Cl-tien-2-ilo, indol-5-ilo, indol-6-ilo, indazol-6-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-indazol-5-ilo, 1-Me-3-NH_2-indazol-6-ilo, 3-NH_2-benzisoxazol-6-ilo, 1,2,3,4-tetrahidroisoquinolin-6-ilo, 1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-COPh-1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-CO_2Bn-1,2,3,4-tetrahidroisoquinolin-3-ilo, 1,2,3,4-tetrahidroisoquinolin-1-on-6-ilo, 2H-isoquinolin-1-on-6-ilo, isoquinolin-6-ilo, 1-NH_2-isoquinolin-6-ilo, 1-NH_2-3-Me-isoquinolin-6-ilo, 1-NH_2-5,6,7,8-tetrahidroisoquinolin-6-ilo, 4-NH_2-quinazolin-7-ilo, 3H-quinazolin-4-on-7-ilo,



R^3 es CO_2H, CO_2Me, -C(O)$NHCH_2CO_2H$, -C(O)$NHCH_2CO_2Et$, -

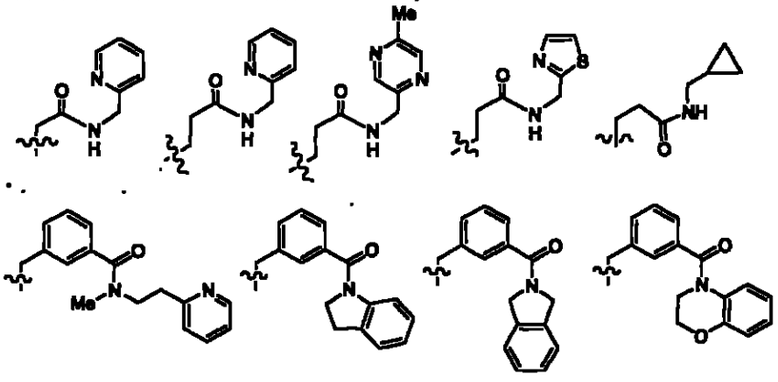
$C(O)NH_2$, -C(O)NHMe, -C(O)NHBn, fenilo, fenetilo, -(CH=CH)-fenilo, 3-bifenilo, 4-bifenilo, 3,4-metilendioxifenilo, 1-naftilo, 2-naftilo, $3-NH_2$-fenilo, $3-NMe_2$-fenilo, 4-OPh-fenilo, 4-OBn-fenilo, 4-(t-butoximetil)-fenilo, $4-SO_2Me$-fenilo, 3-CN-fenilo, 4-CN-fenilo, 3-F-fenilo, 4-F-fenilo, 3-Cl-fenilo, 4-Cl-fenilo, 3-Br-fenilo, 4-Br-fenilo, 3-OH-fenilo, 4-OH-fenilo, 2-OMe-fenilo, 3-OMe-fenilo, 4-OMe-fenilo, $3-CF_3$-fenilo, $4-CF_3$-fenilo, $3-CO_2H$-fenilo, $4-CO_2H$-fenilo, $3-CO_2Me$-fenilo, $4-CO_2Me$-fenilo, $3-CH_2CO_2H$-fenilo, $4-CH_2CO_2H$-fenilo, $4-CH_2CO_2Me$-fenilo, $3-CH_2CO_2Et$-fenilo, $4-CH_2CO_2Et$-fenilo, $3-CONH_2$-fenilo, $4-CONH_2$-fenilo, $3-CH_2CONH_2$-fenilo, $4-CH_2CONH_2$-fenilo, 4-CONHMe-fenilo, $4-CONMe_2$-fenilo, 4-amidino-fenilo, 3-NHCOMe-fenilo, 4-NHCOMe-fenilo, $4-NHCO_2Me$-fenilo $4-SO_2NH_2$-fenilo, $3-NHSO_2Me$-fenilo, $4-NHSO_2Me$-fenilo, 2,4-diF-fenilo, 3-F-4-CN-fenilo, 3-CN-5-F-fenilo, $3-F-4-CONH_2$-fenilo, $3-CO_2H-4$-CN-fenilo, $3-NMe_2-4$-CN-fenilo, $3-Ph-4-CONH_2$-fenilo, 4-(2-oxo-1-piperidino)-fenilo, tiazol-2-ilo, $4-CO_2Me$-tiazol-2-ilo, $4-CONH_2$-tiazol-2-ilo, 1-Bn-piazol-4-ilo, 5-Ph-oxazol-2-ilo, $5-CONH_2$-tien-2-ilo, $5-CO_2H$-tien-2-ilo, pirid-2-ilo, pirid-3-ilo, pirid-4-ilo, $6-NH_2$-Pirid-3-ilo, benzimidazol-2-ilo, 1-Me-benzimidazol-2-ilo, benzoxazol-2-ilo, benzotiazol-2-ilo, $3-NH_2$-benzisoxazol-6-ilo, $3-NH_2$-benzisoxazol-5-ilo, indazol-5-ilo, indazol-6-ilo, $3-NH_2$-

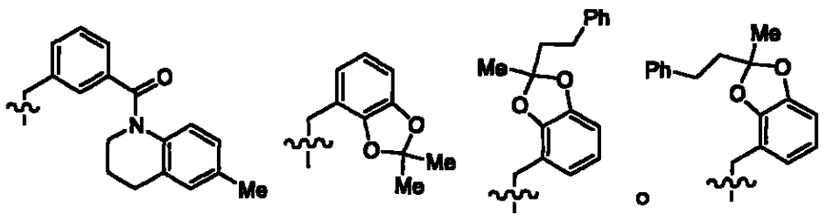
indazol-5-ilo, 3-OH-indazol-5-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-4-F-indazol-6-ilo, 3-NH_2-5-F-indazol-6-ilo, 3-NH_2-7-F-indazol-6-ilo, 4-imino-3,4-dihdiro-2H-ftalazin-1-on-7-ilo, 3-(5-tetrazolil)-fenilo, 2,3d-dihidro-isoindol-1-on-6-ilo, quinolin-5-ilo, quinolin-6-ilo, quinolin-8-ilo, isoquinolin-5-ilo, 2H-isoquinolin-1-on-6-ilo, 2,4-diaminoquinazolin-7-ilo, o 4-NH_2-quinazolin-7-ilo;

R^4 es H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, fenilo, 3-F-4-CN-fenilo, o 3-NH_2-6-indazolilo; y

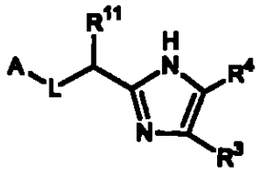
R^{11} es Me, neopentilo, ciclohexilmetilo, -$CH_2CH_2CONHBn$, -$CH_2CH_2CONH(CH_2CH_2Ph)$, -$CH_2CH_2CON(Me)Bn$, bencilo, fenetilo, 2-Me-bencilo, 3-Me-bencilo, 4-Me-bencilo, 2-F-bencilo, 3-F-bencilo, 4-F-bencilo, 2-Cl-bencilo, 3-Cl-bencilo, 4-Cl-bencilo, 2-Br-bencilo, 3-Br-bencilo, 4-Br-bencilo, 3-CF_3-bencilo, 4-CF_3-bencilo, 2-NH_2-bencilo, 3-NH_2-bencilo, 2-NO_2-bencilo, 3-NO_2-bencilo, 4-NO_2-bencilo, 3-OMe-bencilo, 4-OMe-bencilo, 3-OCF_2H-bencilo, 2-OCF_3-bencilo, 3-OCF_3-bencilo, 2-OPh-bencilo, 3-OPh-bencilo, 2-OBn-bencilo, 3-OBn-bencilo, 4-OBn-bencilo, 4-COPh-bencilo, 3-CO_2H-bencilo, 3-CO_2Me-bencilo, 3-NHAc-bencilo, 2-NHCOPh-bencilo, 2-NHCOBn-bencilo, 3-NHCOBn-bencilo, 3-N(Me)COPh-bencilo, 3-(-$NHCOCH_2CH_2Ph$)-bencilo, 2-$NHSO_2Ph$-bencilo, 3-$NHSO_2Ph$-bencilo, 3-[$SO_2N(Me)Ph$)-bencilo, 3-[$N(Me)SO_2Ph$)-bencilo, 3-[CONH(*i*-Bu)]-bencilo, 3-[CONH(*t*-Bu)]-bencilo, 3-[CONH(isopentil)]-bencilo, 3-[CONH(2-Me-Ph)]-bencilo, 3-

[CONH(3-Me-Ph)]-bencilo, 3-[CONH(4-Me-Ph)]-bencilo, 3-[CONH(4-F-Ph)]-bencilo, 3-[CONH(1-naftil)]-bencilo, 3-(CONHBn)-bencilo, 3-[CONH(4-Cl-Bn)]-bencilo, 3-[CONH(4-OMe-Bn)]-bencilo, 3-[CONHCH$_2$CH$_2$Ph]-bencilo, 3-[CONH CH$_2$CH$_2$(4-OMe-Ph)]-bencilo, 3-[CONHCH$_2$CH$_2$(2-Cl-Ph)]-bencilo, 3-[CONHCH$_2$CH$_2$(3-Cl-Ph)]-bencilo, 3-[CONHCH$_2$CH$_2$(4-Cl-Ph)]-bencilo, 3-[CONH(CH$_2$)$_3$Ph]-bencilo, 3-[CONMe$_2$]-bencilo, 3-[CON(Me)(Et)]-bencilo, 3-[CON(Me)(*i*-Pr)]-bencilo, 3-[CON(Me)(*i*-Bu)]-bencilo, 3-[CON(Me)Ph]-bencilo, 3-[CON(Me)(3-Me-Ph)]-bencilo, 3-[CON(Me)(4-Me-Ph)]-bencilo, 3-[CON(Me)Bn]-bencilo, 3-[CON(Me)(3-Cl-Bn)]-bencilo, 3-[CON(Me)(4-Cl-Bn)]-bencilo, 3-[CON(Me)(CH$_2$CH$_2$Ph)]-bencilo, 3-[CON(Et)Ph]-bencilo, 3-[CO(1-piperidino)]-bencilo, 3-[CO(4-Ph-1-piperidino)]-bencilo, 3-[CO(1,2,3,4-tetrahidroisoquinolino)]-bencilo, 2-Ph-bencilo, 3-Ph-bencilo, 4-Ph-bencilo, 3-fenetil-bencilo, -CH$_2$OBn, -CH$_2$SBn, 1-naftilmetilo, 2-naftilmetilo, tiazol-4-ilmetilo, pirid-2-ilmetilo, pirid-3-ilmetilo, pirid-4-ilmetilo, 1-Bn-imidazol-4-ilmetilo, benzotiazol-2-ilmetilo,





En un sexto aspecto, la presente invención incluye un compuesto de la Fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos dentro del alcance del primer aspecto en donde:

R^3 es 3-NH_2-indazol-5-ilo, 3-OH-indazol-5-ilo, 3-NH_2-benzisoxazol-6-ilo, 3-NH_2-benzisoxazol-5-ilo, indazol-5-ilo, indazol-6-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-4-F-indazol-6-ilo, 3-NH2-5-F-indazol-6-ilo, 3-NH_2-7-F-indazol-6-ilo, isoquinolin-5-ilo, quinolin-5-ilo, quinolin-8-ilo, 2H-isoquinolin-1-on-6-ilo, 2,4-diaminoquinazolin-7-ilo, o 4-NH_2-quinazolin-7-ilo.

En un séptimo aspecto, la presente invención incluye compuestos de la fórmula (IIa) dentro del alcance del sexto aspecto en donde:

L es $-C(O)NR^{10}-$ o $-NR^{10}C(O)-$;

R^1 es, independientemente cada que se presenta, F, Cl,

Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t-Bu)$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, -NHEt, $-NHCO_2(t-Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, $-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{10} es, independientemente cada que se presenta, H, Me, bencilo, fenetilo, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, o $-CH_2CH_2CONHCH_2CH_2Ph$;

R^{11} es alquilo C_1-C_6, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$ cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{11b}; y

R^{11b} es, independientemente cada que se presenta, H, F, Cl, Br, CF_3, OMe, OEt, O(i-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-N^8CO_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-SO_2R^C$, alquilo C_1-C_4-, Ph, o Bn.

En un octavo aspecto, la presente invención incluye compuestos de la Fórmula (II), dentro del alcance del séptimo

aspecto en donde:

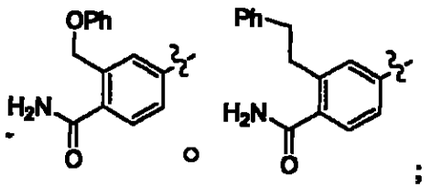
A es substituido con 0-1 R^1 y 0-2 R^2 y son seleccionados de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo; y

R^{10} es H.

En un noveno aspecto, la presente invención incluye compuestos de la Fórmula (II), dentro del alcance del octavo aspecto en donde:

A es 4-CH_2NH_2-ciclohexilo, 4-CO_2Me-ciclohexilo, 4-$CONH_2$-ciclohexilo, 4-$NHCO_2$(t-Bu)-ciclohexilo, 4-$NHCO_2$Bn-ciclohexilo, fenilo, 4-Me-fenilo, 3-OMe-fenilo, 4-CH_2NH_2-fenilo, 3-$CONH_2$-fenilo, 4-$CONH_2$-fenilo, 3-amidino-fenilo, 4-amidino-fenilo, 2-F-4-Me-fenilo, 2-Bn-4-CH_2NH_2-fenilo, 4-SO_2NH_2-fenilo, 2-F-5-OMe-fenilo, 2-F-4-Cl-fenilo, 2-F-4-CH_2NH_2-fenilo, 2-F-4-$CONH_2$-fenilo, 2-Cl-4-$CONH_2$-fenilo, 2-Et-4-CH_2NH_2-fenilo, 2-NHEt-4-CH_2NH_2-fenilo, 2-OMe-4-$CONH_2$-fenilo, 3-OMe-4-$CONH_2$-fenilo, 1,2,3,4-tetrahidronaft-2-ilo, 3-Cl-tien-2-ilo, indol-5-ilo, indol-5-ilo, indazol-5-ilo, indazol-6-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-indazol-5-ilo, 1-Me-3-NH_2-indazol-6-ilo, 3-NH_2-benzisoxazol-6-ilo, 1,2,3,4-tetrahidroisoquinolin-6-ilo,

1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-COPh-1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-CO_2Bn-1,2,3,4-tetrahidroisoquinolin-3-ilo, 1,2,3,4-tetrahidroisoquinolin-1-on-6-ilo, 2H-isoquinolin-1-on-6-ilo, isoquinolin-6-ilo, 1-NH_2-isoquinolin-6-ilo, 1-NH_2-3-Me-isoquinolin-6-ilo, 1-NH_2-5,6,7,8-tetrahidroisoquinolin-6-ilo, 4-NH_2-quinazolin-7-ilo, 3H-quinazolin-4-on-7-ilo,

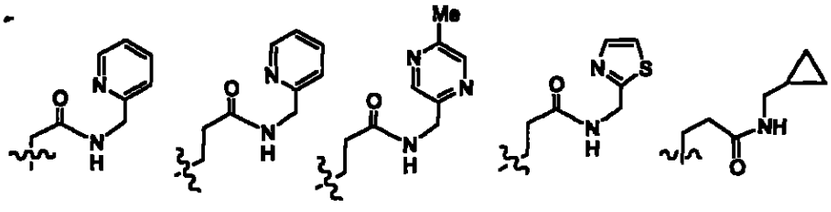


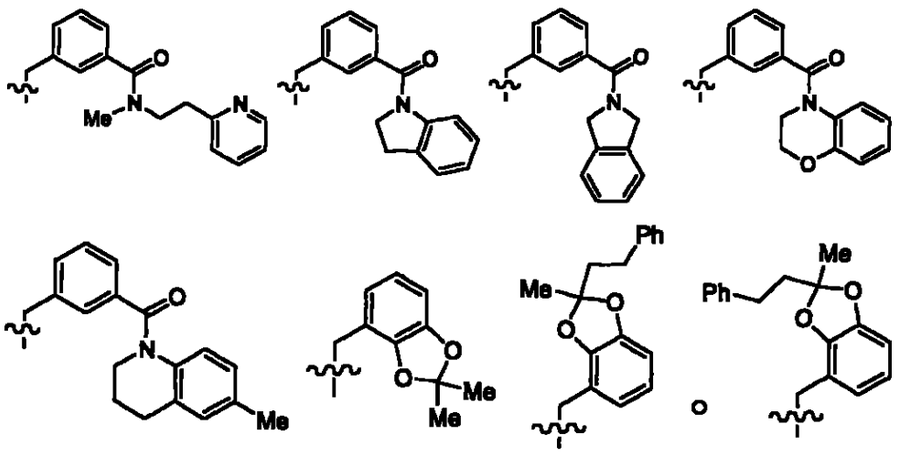
;

R^4 es H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, fenilo, 3-F-4-CN-fenilo, o 3-NH_{2-6}-indazolilo; y

R^{11} es Me, neopentilo, ciclohexilmetilo, -$CH_2CH_2CONHBn$, -$CH_2CH_2CONH(CH_2CH_2Ph)$, -$CH_2CH_2CON(Me)Bn$, bencilo, fenetilo, 2-Me-bencilo, 3-Me-bencilo, 4-Me-bencilo, 2-F-bencilo, 3-F-bencilo, 4-F-bencilo, 2-Cl-bencilo, 3-Cl-bencilo, 4-Cl-bencilo, 2-Br-bencilo, 3-Br-bencilo, 4-Br-bencilo, 3-CF_3-bencilo, 4-CF_3-bencilo, 2-NH_2-bencilo, 3-NH_2-bencilo, 2-NO_2-bencilo, 3-NO_2-bencilo, 4-NO_2-bencilo, 3-OMe-bencilo, 4-OMe-bencilo, 3-OCF_2H-bencilo, 2-OCF_3-bencilo, 3-OCF_3-bencilo, 2-OPh-bencilo, 3-OPh-bencilo, 2-OBn-bencilo, 3-OBn-bencilo, 4-OBn-bencilo, 4-COPh-bencilo, 3-CO_2H-bencilo, 3-CO_2Me-bencilo, 3-NHAc-bencilo, 2-NHCOPh-bencilo, 2-NHCOBn-bencilo, 3-NHCOBn-bencilo, 3-N(Me)COPh-bencilo, 3-(-$NHCOCH_2CH_2Ph$)-bencilo, 2-

ÑHSO$_2$Ph-bencilo, 3-NHSO$_2$Ph-bencilo, 3-[SO$_2$N(Me)Ph]-bencilo, 3-[N(Me)SO$_2$Ph]-bencilo, 3-[CONH(*i*-Bu)]-bencilo, 3-[CONH(*t*-Bu)]-bencilo, 3-[CONH(isopentil)]-bencilo, 3-[CONH(2-Me-Ph)]-bencilo, 3-[CONH(3-Me-Ph)]-bencilo, 3-[CONH(4-Me-Ph)]-bencilo, 3-[CONH(4-F-Ph)]-bencilo, 3-[CONH(1-naftil)]-bencilo, 3-(CONHBn)-bencilo, 3-[CONH(4-Cl-Bn)]-bencilo, 3-[CONH(4-OMe-Bn)]-bencilo, 3-[CONHCH$_2$CH$_2$Ph]-bencilo, 3-[CONHCH$_2$CH$_2$(4-OMe-Ph)]-bencilo, 3-[CONHCH$_2$CH$_2$(2-Cl-Ph)]-bencilo, 3-[CONHCH$_2$CH$_2$(3-Cl-Ph)]-bencilo, 3-[CONHCH$_2$CH$_2$(4-Cl-Ph)]-bencilo, 3-[CONH(CH$_2$)$_3$Ph]-bencilo, 3-[CONMe$_2$]-bencilo, 3-[CON(Me)(Et)]-bencilo, 3-[CON(Me)(*i*-Pr)]-bencilo, 3-[CON(Me)(*i*-Bu)]-bencilo, 3-[CON(Me)Ph]-bencilo, 3-[CON(Me)(3-Me-Ph)]-bencilo, 3-[CON(Me)(4-Me-Ph)]-bencilo, 3-[CON(Me)Bn]-bencilo, 3-[CON(Me)(3-Cl-Bn)]-bencilo, 3-[CON(Me)(4-Cl-Bn)]-bencilo, 3-[CON(Me)(CH$_2$CH$_2$Ph)]-bencilo, 3-[CON(Et)Ph]-bencilo, 3-[CO(1-piperidino)]-bencilo, 3-[CO(4-Ph-1-piperidino)]-bencilo, 3-[CO(1,2,3,4-tetrahidroisoquinolino)]-bencilo, 2-Ph-bencilo, 3-Ph-bencilo, 4-Ph-bencilo, 3-fenetil-bencilo, -CH$_2$OBn, -CH$_2$SBn, 1-naftilmetilo, 2-naftilmetilo, tiazol-4-ilmetilo, pirid-2-ilmetilo, pirid-3-ilmetilo, pirid-4-ilmetilo, 1-Bn-imidazol-4-ilmetilo, benzotiazol-2-ilmetilo,





En un décimo aspecto, la presente invención incluye los compuestos de la fórmula (II), dentro del alcance del octavo aspecto en donde:

A es 4-CH_2NH_2-ciclohexilo, 4-$NHCO_2$(t-Bu)-ciclohexilo, 4-$NHCO_2$Bn-ciclohexilo, o 1-NH_2-5,6,7,8-tetrahidroisoquinolin-6-ilo;

L es -C(O)NH- o NHC(O)-;

R^3 es indazol-5-ilo, indazol-6-ilo, 3-NH_2-indazol-5-ilo, 3-OH-indazol-5-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-4-F-indazol-6-ilo, 3-NH_2-5-F-indazol-6-ilo, 3-NH_2-7-F-indazol-6-ilo, o 4-NH_2-quinazolin-7-ilo;

R^4 es H, Me, F, Br, Cl, o CF_3; y

R^{11} es bencilo substituido con 0-2 R^{11b}.

En un decimoprimer aspecto, la presente invención incluye compuestos de la fórmula (II), dentro del alcance del décimo aspecto en donde:

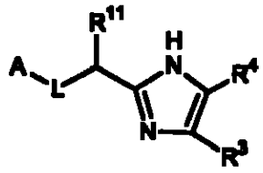
A es 4-CH_2NH_2-ciclohexilo;

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L es $-C(O)NH-$; y

R^3 es 3-NH_2-indazol-6-ilo o 4-NH_2-quinazolin-7-ilo.

En un decimosegundo aspecto, la presente invención incluye un compuesto de la fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos, dentro del alcance del primer aspecto en donde:

A es substituido con 0-2 R^1 y 0-1 R^2 y seleccionados de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

L es $-C(O)NR^{10}-$ o $-NR^{10}C(O)-$;

R^3 es $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, -

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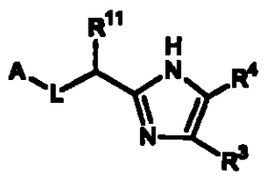
$CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b}; y

R^{11} es bencilo substituido con 0-2 R^{11b}.

En otro aspecto, la presente invención incluye un compuesto de la fórmula (II), dentro del alcance del decimosegundo aspecto en donde:

R^3 es $-(CH_2)_r-$ heterociclo biciclico de 9 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a}.

En un decimotercer aspecto, la presente invención incluye un compuesto de la fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables del mismo dentro del alcance del primer aspecto en donde:

A está substituido con 0-1 R^1 y 0-2 R^2 y se selecciona de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-

tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

L es $-C(O)NR^{10}-$ o $-NR^{10}C(O)-$;

R^3 es $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d};

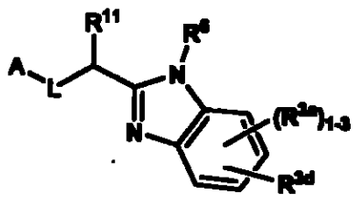
R^4 es, independientemente cada que se presenta, H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, fenilo, 3-F-4-CN-fenilo, o 3-NH_2-6-indazolilo; y

R^{11} es bencilo substituido con 0-2 R^{11b}.

En otro aspecto, la presente invención incluye un compuesto de la fórmula (II), dentro del alcance del decimotercer aspecto en donde:

R^3 es -(CH2)r- fenilo substituido con 0-3 R^{3a}.

En un decimocuarto aspecto, la presente invención incluye un compuesto de la fórmula (III):



(III)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos, dentro del alcance del primer aspecto en donde:

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, Me, CN, OH, NH_2, OMe, O(t-Bu), OBn, CF_3, CO_2H, CO_2Me, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, -NHCOMe, $-CONH_2$, $-CH_2CONH_2$, -CONHMe, $-CONMe_2$, $-C(=NH)NH_2$, $-NR^7R^8$, $-SO_2Me$, $-SO_2NH_2$, Ph, o 2-oxo-piperidin-1-ilo;

R^{3d} es H o alquilo C_{1-4};

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprenden: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_r-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{11a}, alquenilo C_{2-6} substituido con 0-2 R^{11a}, alquinilo C_{2-6} substituido con 0-2 R^{11a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b}.

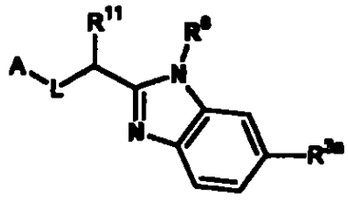
En un decimoquinto aspecto, la presente invención incluye compuestos de la formula (III), dentro del alcance del decimocuarto aspecto en donde:

R^1 es, independientemente cada que se presenta, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, o $-CH_2CH_2NH_2$;

R^{10} es H, Me, bencilo, o fenetilo; y

R^{11} es Me, $-(CH_2)_r$-fenilo substituido con 0-1 R^{11b}, o $-(CH_2)r$-heteroarilo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-1 R^{11b}.

En un decimosexto aspecto, la presente invención incluye compuestos de la fórmula (IV):



(IV)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos, dentro del alcance del primer aspecto en donde:

A es ciclohexilo substituido con 1 R^1, fenilo substituido con 1 R^1, piridilo substituido con 1 R^1, naftilo substituido con 1 R^1, benzisoxazol substituido con 1 R^1, o isoquinolinilo substituido con 0-1 R^1;

L es $-C(O)NH-$, $-C(O)NMe-$, $-C(O)N(bencilo)-$, $-C(O)N(fenetilo)-$, $-NHC(O)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, o $-NHC(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-$

$C(=NH)NH_2$, $-C(O)NH_2$, o $-CH_2NH_2$;

R^{3a} es F, Cl, Br, Me, CN, OMe, CF_3, CO_2H, CO_2Me, CO_2Et, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, $CONH_2$, $-CONHMe$, $-CON(Me)_2$, $-CH_2CONH_2$, o $-C(=NH)NH_2$;

R^6 es H;

R^{10} es H, Me, bencilo, o fenetilo; y

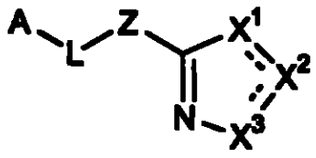
R^{11} es Me, $-(CH_2)r$-fenilo substituido con 0-1 R^{11b}, o $-(CH_2)_r$ heteroarilo de 5-10 miembros substituidos con 0-1 R^{11b} y se selecciona de tiazolilo, imidazolilo, piridilo, y benzotiazolilo.

En un decimoséptimo aspecto, la presente invención incluye compuestos de la fórmula (IV), dentro del alcance del decimosexto aspecto en donde:

A es 4-CH_2NH_2-ciclohexilo o 4-amidino-fenilo; y

R^{3a} es, independientemente cada que se presenta, CO_2H, CO_2Me, $-CH_2CO_2H$, $-CH_2CO_2Et$, $-CONH_2$, o $-CH_2CONH_2$.

En un decimoctavo aspecto, la presente invención proporciona, *inter alia*, un compuesto de la fórmula (V):

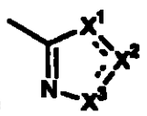
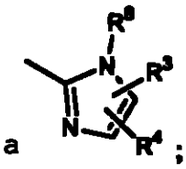


(V)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos, en donde:

A es carbociclo C_{3-10} substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no esta unido a L por medio de cualquiera de los átomos de nitrógeno en el anillo A;

X^1, X^2 y X^3 son cada uno independientemente CR^3, CR^4, CR^4CR^5, O, $S(O)_p$ N, NR^3, NR^6 o C(O); con la condición de que ningún enlace S-S, S-O, o O-O está presente en el anillo;

con la condición de que  es diferente a  ;

Z es $-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-(CH_2)-$, $-NR^{13}-$, o $-NR^{13}CH_2-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)_pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, o $-C(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-NH$(alquilo C_{1-3}), $-N$(alquilo C_{1-3})$_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH^2)_rNR^7R^8$, $-(CH_2)_rNR^7C(O)OR^a$, $-CH_2NH_2$, -

CH_2NH(alquilo C_{1-3}), $-CH_2N$(alquilo $C_{1-3})_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH$(alquilo C_{1-3}), $-CH_2CH_2N$(alquilo $C_{1-3})_2$, -CH(alquilo C_{1-4})NH_2, -C(alquilo $C_{1-4})_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-ciclopropilo, o alquilo C_{1-6} substituido con 0-1 R^{1a};

R^{1a} es H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^2 es, independientemente cada que se presenta, H, =O, F, CI, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{2a}, alquenilo C_{2-6} substituido con 0-2 R^{2a}, alquinilo C_{2-6} substituido con 0-2 R^{2a}, $-(CH_2)$r-carbociclo C_{3-10} substituido con 0-3 R^{2b}, o $-(CH_2)_r$- heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{2b};

R^{2a} es, independientemente cada que se presenta, H, F, CI, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{2b} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, -

$OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

alternativamente, cuando los grupos R^1 y R^2 son substituidos en atomos en el anillo adyacente, estos pueden tomarse juntos con los átomos en el anillo al cual se enlazan para formar un carbociclo o heterociclo de 5 hasta 7 miembros que comprende: átomos de carbono y 0-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el carbociclo o heterociclo es substituido con 0-2 R^{2b};

R^3 es, independientemente cada que se presenta, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$- carbociclo C_{3-10} substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-C(O)-$alquilo C_{1-4}, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, haloalquilo C_{1-4}, haloalcoxi

C_{1-4}, alquilo C_{1-6} substituido por R^{3d}, alquenilo C_{2-6} substituido por R^{3d}, alquinilo C_{2-6} substituido por R^{3d}, cicloalquilo C_{3-6} substituido por 0-1 R^{3d}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

alternativamente, cuando dos grupos R^{3a} se localizan en átomos adyacentes, se toman junto con los átomos a los cuales se enlazan para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3d};

R^{3b} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3c} es, independientemente cada que se presenta, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$ carbocilo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4

heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3d} es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_pR^c$, $-(CF_2)_rCF^3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, alquinilo C_{2-6} substituido con 0-2 R^e, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^4 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{4b}, o $-(CH_2)_r$ heterociclo 5 de 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{4a} es, independientemente cada que se presenta, H, F, =O, alquilo C_{1-6}, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, -

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$NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{4b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^C$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

alternativamente, cuando los grupos R^3 y R^4 se localizan en átomos adyacentes, pueden tomarse juntos para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3d};

R^5 es, independientemente cada que se presenta, H, F, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{5a}, alquenilo C_{2-6} substituido con 0-2 R^{5a}, alquinilo C_{2-6} substituido con 0-2 R^{5a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{5b}, o $-(CH_2)_r$ heterociclo 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{5b};

R^{5a} es, independientemente cada que se presenta, H, =O, OR^a, SR^a, F, Cl, Br, I, CF_3, OCF_3, CN, NO_2, $-NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{5b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, haloalquilo C_{1-4}, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, $-S(O)_2R^c$, o $-(CH_2)_r$ fenilo substituido con 0-3 R^d;

R^7 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n$-carbociclo C_{3-10}, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(arilo C_{6-10}); en donde el alquilo, carbociclo, heteroarilo, y arilo son opcionalmente substituidos con 0-2 R^f;

R^8 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo, o $-(CH_2)_n$- heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde el alquilo, fenilo y heterociclo son opcionalmente substituidos con 0-2 R^f;

alternativamente, R^7 y R^8, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d;

R^{8a} es, independientemente cada que se presenta, H, OH, alquilo C_{1-6}, alcoxi C_{1-4}, (arilo C_{6-10})-alcoxi C_{1-4}, $-(CH_2)_n$-fenilo, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(alquilo C_{1-4}), o $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(arilo C_{6-10}); en donde el fenilo, arilo, y heteroarilo es opcionalmente substituido con 0-2 R^f;

R^9 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo; en donde el alquilo y fenilo son opcionalmente substituidos con 0-2 R^f;

R^{9a} es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

alternativamente, R^8 y R^9, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3R^{10a}, alquenilo C_{2-6} substituido con 0-3 R^{10a}, alquinilo C_{2-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^{10a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, -

$C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C-$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CR^{14}R^{15})_r$ carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CR^{14}R^{15})_r$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b};

R^{11a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, CF_3, SR^a, F, CN, NO_2, NR^7R^8, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^C$, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^d;

R^{11b} es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^C$, $-SO_2R^C$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^C$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y

$S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales se enlazan para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g;

R^{12} es, independientemente cada que se presenta, H, F, o alquilo C_{1-4};

R^{13} es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n$-fenilo, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)OR^c$, $-CONR^eR^c$, $-OCONR^eR^c$, $-S(O)_2R^c$, $-C(O)O$-(alquilo C_{1-4})$-OC(O)$-(alquilo C_{1-4}), o $-C(O)O$-(alquilo C_{1-4})$-OC(O)$-(arilo C_{6-10}); en donde el alquilo, fenilo, heteroarilo, arilo son opcionalmente substituidos con 0-2 R^f;

R^{14} y R^{15} son, independientemente cada que se presenta, H, F, o alquilo C_{1-4};

alternativamente, R^{14} se combina con R^{15} para formar =O;

R^a es, independientemente cada que se presenta, H, CF_3, alquilo C_{1-6}, $-(CH_2)_r$- cicloalquilo C_{3-7}, $-(CH_2)_r$ arilo C_{6-10}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los grupos cicloalquilo, arilo y heteroarilo son opcionalmente substituidos con 0-2 R^f.

R^b es, independientemente cada que se presenta, CF_3, OH,

alcoxi C_{1-4}, alquilo C_{1-6}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^c es, independientemente cada que se presenta, CF_3, alquilo C_{1-6} substituido con 0-2 R^f, cicloalquilo C_{3-6} substituido con 0-2 R^f, arilo C_{6-10}, heteroarilo de 5 hasta 10 miembros, (arilo C_{6-10})-alquilo C_{1-4}, o (heteroarilo de 5 hasta 10 miembros)-alquilo C_{1-4}, en donde los grupos arilo y heteroarilo son opcionalmente substituidos con 0-3 R^f;

R^d es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, o alquinilo C_{2-6} substituido con 0-2 R^e;

R^e es, independientemente cada que se presenta, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^f es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, -

$NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-alquilo C_{1-4}, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, o $-(CH_2)_n$-fenilo;

R^g es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

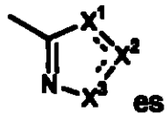
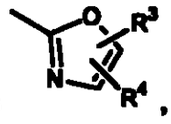
n, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4;

p, cada que se presenta, se selecciona de 0, 1, y 2;

r, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4; y

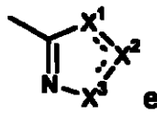
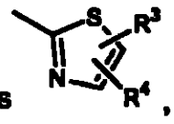
s, cada que se presenta, se selecciona de 1, 2, 3, y 4;

con la condición de que:

(a). cuando el grupo  es  ,

i. y cuando L es $-NHC(O)-$, R^{14} no se combina con R^{15} para formar =O;

ii. y cuando L es $-C(O)NH-$ y A es fenilo, R^1 no es $-NHC(O)H$;

(b). cuando el grupo  es  ,

i. y cuando L es $-NHC(O)-$ y R^3 se combina con R^4 para formar un anillo fenilo fusionado con el tiazol, el enillo fenilo es subsituido con al menos un R^{3a};

ii. y cuando L es -C(O)NH- y A es fenilo, R^1 no es -NHC(O)H; y

(c). A no es oxazolinona, tiofeno, oxadiazol o furano substituidos o no substituidos.

En un decimonoveno aspecto de la presente invención incluye compuestos de la Fórmula (V), dentro del alcance del decimoctavo aspecto en donde:

A es cicloalquilo C_{3-8} substituido con 0-1 R^1 y 0-3 R^2, cicloalquenilo C_{4-8} substituido con 0-1 R^1 y 0-3 R^2, fenilo substituido con 0-1 R^1 y 0-3 R^2, naftilo substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no es unido a L por medio de los átomos de nitrógeno en el anillo A;

Z es $-C(R^{11})(R^{12})-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, o $-NR^{10}C(O)CH_2-$;

R^3 es, independientemente cada que se presenta, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-cicloalquilo C_{3-8} substituido con 0-2 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo de 5-10 miembros

que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde

el heterociclo es substituido con 0-3 R^{11b}.

En un vigésimo aspecto, la presente invención incluye compuestos de la Fórmula (V), dentro del alcance del decimoctavo del aspecto en donde:

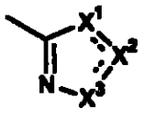
A es cicloalquilo C_{5-6} substituido con 0-1 R^1 y 0-2 R^2, cicloalquenilo C_{5-6} substituido con 0-1 R^1 y 0-2 R^2, fenilo substituido con 0-1 R^1 y 0-3 R^2, naftilo substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no es unido a L por medio a cualquiera de los átomos de nitrógeno en el anillo A;

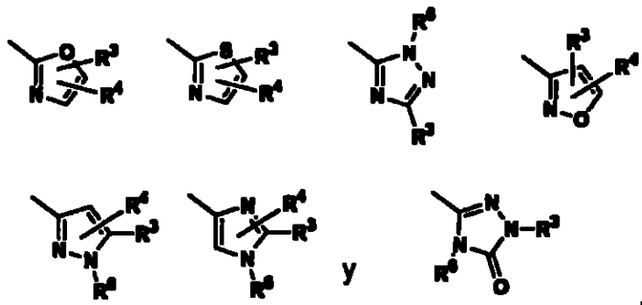
R^3 es, independientemente cada que se presenta, $-(CH_2)_r-C(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r-$fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r-$naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r-$indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r-$heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d}; y

R^6 es, independientemente cada que se presenta, H o alquilo C_{1-6}.

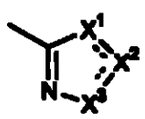
En un vigésimo primer aspecto, la presente invención

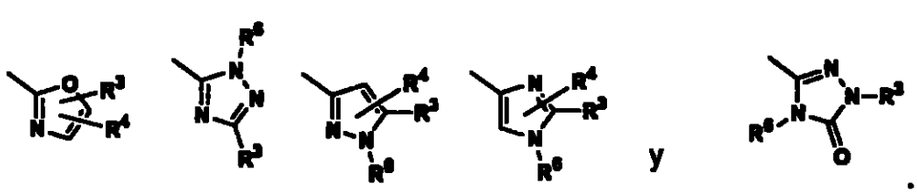
incluye compuestos de la Fórmula (V), dentro del alcance del decimoctavo aspecto en donde:

el grupo  se selecciona de:



En un vigésimo segundo aspecto, la presente invención incluye compuestos de la Fórmula (V), dentro del alcance del decimoctavo aspecto en donde:

el grupo  se selecciona de:

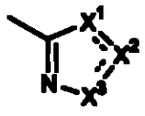


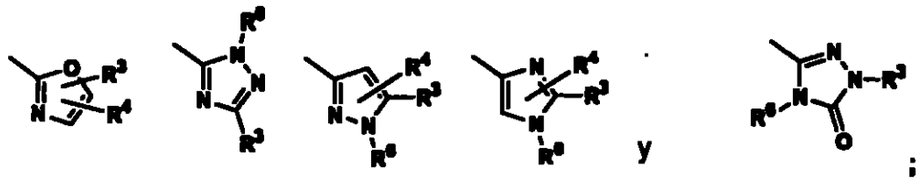
En un vigésimo tercer aspecto, la presente invención incluye compuestos de la Fórmula (V), dentro del alcance del decimoctavo aspecto en donde:

A es substituido con 0-1 R^1 y 0-2 R^2 y seleccionados de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-

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tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

el grupo  se selecciona de:



Z es $-CH(R^{12})-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, o $-NR^{10}C(O)CH_2-$;

R^3 es, independientemente cada que se presenta, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d} o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y S(O)p, y substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2

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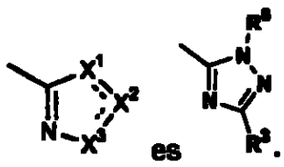
R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^{4b}.

R^6 es H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

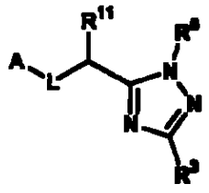
R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d; y

R^{12} es, independientemente cada que se presenta, H, F, o Me.

En otro aspecto, la presente invención incluye compuestos de la Fórmula (V), dentro del alcance de vigésimo segundo aspecto en donde.

el grupo  es .

En un vigésimo cuarto aspecto, la presente invención incluye un compuesto de la fórmula (VI):



(VI)

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o sus estereoisómeros, tautómeros, sales, solvatos, o profármacos farmacéuticamente aceptable del mismo dentro del alcance del decimoctavo aspecto en donde:

R^3 es $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_sC(O)NR^8(CH^2)_rCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{3a}, $-(CH_2)_r$-indanilo substituido con 0-2 R^{3a}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6}, substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es

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substituido con 0-3 R^{11b}.

En un vigésimo quinto aspecto, la presente invención incluye compuestos de la Fórmula (VI), dentro del alcance del vigésimo cuarto aspecto en donde:

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-CMe_2NH_2$, $-NHEt$, $-NHCO_2(t\text{-}Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)_r$fenilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, naftilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, indanilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, o un $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-2 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a} y 0-1 R^{3d};

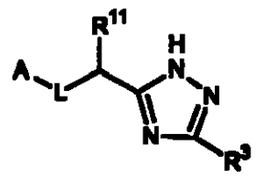
R^6 es H;

R^{10} es, independientemente cada que se presenta, H, Me, bencilo, fenetilo, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, o $-CH_2CH_2CONHCH_2CH_2Ph$; y

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es

substituido con 0-2 R^{11b}.

En un vigésimo sexto aspecto, la presente invención incluye los compuestos de la Fórmula (VII):



(VII)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos del mismo farmacéuticamente aceptable dentro del alcance del decimoctavo aspecto en donde:

A es substituido con 0-2 R^1 y 0-1 R^2 y seleccionado de: cicloalquilo C_{3-7}, fenilo naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

L es -C(O)NH- o -NHC(O)-;

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t-Bu)$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t-Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, -

$C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, fenilo substituido con 0-2 R^{3a}, naftilo substituido con 0-2 R^{3a}, indanilo substituido con 0-2 R^{3a}, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-2 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a};

R^4 es H, F, Cl, Br, CF_3, CO_2H, CO_2Me, CO_2Et, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{4b};

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$-heteroarilo de 5 hasta 10 miembros substituidos con 0-2 R^{11b} y seleccionados de tiazolilo, oxazolilo, triazolilo, tetrazolilo, imidazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, benzimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, tetrahidroquinolinilo, y tetrahidroisoquinolinilo;

R^{11b} es, independientemente cada que se presenta, H, F, Cl, Br, CF_3, OMe, OEt, O(i-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, alquilo C_1-C_4-, Ph, o Bn;

alternativamente, cuando dos grupos R^{11b} son

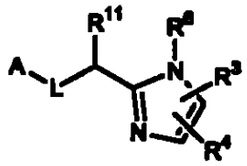
substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales están enlazados para formar un heterociclo 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g.

En un vigésimo séptimo aspecto, la presente invención incluye compuestos de la fórmula (V), dentro del alcance del vigésimo sexto aspecto en donde:

A es 4-CH_2NH_2-ciclohexilo o 4-amidino-fenilo; y

R^3 es fenilo, 3-CN-fenilo, 4-CN-fenilo, 3-Br-fenilo, 4-Br-fenilo, 3-OMe-fenilo, 4-OMe-fenilo, 3-CF_3-fenilo, 4-CF_3-fenilo, 3-CO_2H-fenilo, 4-CO_2H-fenilo, 4-CO_2Me-fenilo, 4-CH_2CO_2H-fenilo, 4-CH_2CO_2Me-fenilo, 3-$CONH_2$-fenilo, 4-$CONH_2$-fenilo, 4-CONHMe-fenilo, 4-$CON(Me)_2$-fenilo, 4-CH_2CONH_2-fenilo, 4-amidino-fenilo, o 2,4-diF-fenilo.

En un vigésimo octavo aspecto, la presente invención incluye, *inter alia*, un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (I):



(I)

o sus estereoisómeros, tautómeros, sales solvatos o profármacos farmacéuticamente aceptable del mismo, en donde:

A es carbociclo C_{3-10} substituido con 0-3 R^1 y 0-1 R^2, o con un heterociclo de 5 hasta 12 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^1 y 0-1 R^2;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)_pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, o $-C(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-NH$(alquilo C_1-C_3), $-N$(alquilo $C_1-C_3)_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7CO_2R^a$, $-CH_2NH_2$, $-CH_2NH$(alquilo C_{1-3}), $-CH_2N$(alquilo $C_{1-3})_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH$(alquilo C_1-C_3), $-CH_2CH_2N$(alquilo $C_{1-3})_2$, $-CH$(alquilo C_{1-4})NH_2, $-C$(alquilo $C_{1-4})_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-ciclopropilo, o alquilo C_{1-6} substituido con 0-1 R^{1a};

R^{1a} es H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^2 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} substituido con 0-2 R^{2a}, alquenilo C_{2-6} substituido con 0-2 R^{2a}, alquinilo C_{2-6} substituido con 0-2 R^{2a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{2b}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{2b};

R^{2a} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$, $-S(O)R^c$, o $-S(O)_2R^c$;

R^{2b} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, CF_3, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^c$, $-NR^8SO_2NR^8R^9$, $-NR^8SO^2R^c$, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

Alternativamente, cuando los grupos R^1 y R^2 son substituidos en átomos de anillo adyacente, estos pueden tomarse junto con los átomos en el anillo a los cuales se enlazan para formar un un carbociclo o heterociclo de 5 a 7 miembros que comprende: átomos de carbono y 0-4 heteroátomos

seleccionados de N, O, y $S(O)_p$, en donde el carbociclo o heterociclo está substituido con 0-2 R^{2b};

R^3 es F, Cl, Br, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, SR^{3b}, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, alquilo C_{1-4}-C(O)-, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, haloalquilo C_{1-4}, haloalcoxi C_{1-4}-, alquilo C_{1-6} substituido por R^{3d}, alquenilo C_{2-6} substituido por R^{3d}, alquinilo C_{2-6} substituido por R^{3d}, cicloalquilo C_{3-6} substituido por 0-1 R^{3d}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3d};

alternativamente, cuando dos grupos R^{3a} se localizan en átomos adyacentes, estos pueden tomarse junto con los átomos

a los cuales están enlazados para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3d};

R^{3b} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3c} es, independientemente cada que se presenta, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3d};

R^{3d} es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_pR^c$, $-(CF_2)_rCF_3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, alquinilo C_{2-6} substituido con 0-2 R^e, $-(CH_2)_r$- carbociclo C_{3-10} substituido

con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

R^4 es H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{4b}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{4a} es, independientemente cada que se presenta, H, F, =O, alquilo C_{1-6}, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{4b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^C$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4}-;

alternativamente, cuando grupos R^3 y R^4 se localizan en átomos adyacentes, pueden tomarse juntos para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo 5

hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3d};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, haloalquilo C_{1-4}, $-CH_2OR^a$, $-C(O)_2R^C$, $-S(O)_2R^C$ o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^7 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n$-carbociclo C_{3-10}, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^C$, $-CHO$, $-C(O)_2R^C$, $-S(O)_2R^C$, $-CONR^BR^C$, $-OCONHR^C$, $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(alquilo C_{1-4}), o $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(arilo C_{6-10}); en donde los alquilo, carbociclo, heteroarilo, y arilo están substituidos opcionalmente con 0-2 R^f;

R^8 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo, o $-(CH_2)_n$- heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los alquilo, fenilo y heterociclo están substituidos opcionalmente con 0-2 R^f;

alternativamente, cuando R^7 y R^8, se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionalse seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^d;

R^{8a} es, independientemente cada que se presenta, H, OH, alquilo C_{1-6}, alcoxi C_{1-4}, (arilo C_{6-10})-alcoxi C_{1-4}, $-(CH_2)_n$-

fenilo, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(alquilo C_{1-4}), o $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(arilo C_{6-10}); en donde los fenilo, arilo, y heteroarilo están opcionalmente substituidos con 0-2 R^f;

R^9 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo; en donde el alquilo y fenilo están substituidos opcionalmente con 0-2 R^f;

R^{9a} es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

alternativamente, cuando R^8 y R^9, se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, alquenilo C_{2-6} substituido con 0-3 R^{10a}, alquinilo C_{2-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

R^{10a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c$-, $-S(O)R^c$, o $-S(O)_2R^c$;

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CR^{14}R^{15})_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CR^{14}R^{15})_r$-heterociclo 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{11b};

R^{11a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, CF_3, SR^a, F, CN, NO_2, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^C$, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}-, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^d;

R^{11b} es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^C$, $-SO_2R^C$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^C$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)r$- heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

alternativamente, cuando dos grupos R^{11b} son

substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales están enlazados para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g;

R^{14} y R^{15} son, independientemente cada que se presentan, H, F, o alquilo C_{1-4};

alternativamente, R^{14} se combina con R^{15} para formar =O;

R^a es, independientemente cada que se presenta, H, CF_3, alquilo C_{1-6}, $-(CH_2)_r$-cicloalquilo C_{3-7}, $-(CH_2)_r$-arilo C_{6-10}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los grupos cicloalquilo, arilo y heterociclo son opcionalmente substituidos con 0-2 R^f;

R^b es, independientemente cada que se presenta, CF_3, OH, alcoxi C_{1-4}, alquilo C_{1-6} $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^c es, independientemente cada que se presenta, CF_3, alquilo C_{1-6} substituido con 0-2 R^f, cicloalquilo C_{3-6} substituido con 0-2 R^f, arilo C_{6-10}, heteroarilo de 5 hasta 10 miembros, (arilo C_{6-10})-alquilo C_{1-4}, o (heteroarilo de 5 hasta 10 miembros) alquilo C_{1-4}, en donde los grupos arilo y

heteroarilo son opcionalmente substituidos con 0-3 R^f;

R^d es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, o alquinilo C_{2-6} substituido con 0-2 R^e;

R^e es, independientemente cada que se presenta, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^f es, independientemente cada que se presenta, H, =O, $-(CH_2)_r-OR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-alquilo C_{1-4}, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, o $-(CH_2)_n$-fenilo;

R^g es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

n, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4;

p, cada que se presenta, se selecciona de 0, 1, y 2;

r, cada que se presenta, se selecciona de 0, 1, 2, 3, y

4; y

s, cada que se presenta, se selecciona de 1, 2, 3, y 4.

En un vigésimo noveno aspecto, la presente invención proporciona un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (I), dentro del alcance del vigésimo octavo aspecto en donde:

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2CONR^{10}-$, o $-NR^{10}COCH_2-$;

R^3 es $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^6 es H, alquilo C_{1-6}, $-CH_2OR^a$, o $-(CH_2)_r$-fenilo

substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_r-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{11a}, alquenilo C_{2-6} con 0-2 R^{11a}, alquinilo C_{2-6} substituido con 0-2 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$- heterociclo de 5 hasta 10-miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b}.

En un trigésimo aspecto, la presente invención proporciona un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (I), dentro del alcance del vigésimo octavo aspecto en donde:

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, -NHEt, $-NHCO_2(t\text{-}Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a o $-CH_2OR^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, -

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$C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)_r$-fenilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, naftilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, indanilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, $-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

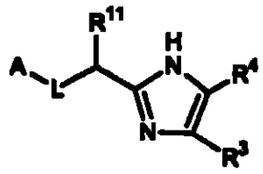
R^6 es H, Me bencilo, o fenetilo;

R^{10} es, independientemente cada que se presenta, H, Me, bencilo, fenetilo, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, o $-CH_2CH_2CONHCH_2CH_2Ph$; y

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{11b}.

En un trigésimo primer aspecto, la presente invención proporciona un método para tratar un trastorno tromboembólico

o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos, dentro del alcance del primer aspecto en donde:

A es substituido con 0-1 R^1 y 0-2 R^2 y seleccionado de: cicloalquilo C_{3-7}, fenilo naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

L es -C(O)NH-, -C(O)NMe-, -C(O)N(bencilo)-, -C(O)N(fenetilo)-, -NHC(O)-, $S(O)_2NH$-, $-CH_2C(O)NH$-, $-C(O)NHCH_2$- $-CH_2NHC(O)$- o $-NHC(O)CH_2$-;

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t\text{-}Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, fenilo substituido con 0-2 R^{3a}, naftilo substituido con 0-2 R^{3a}, indanilo substituido con 0-2 R^{3a}, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-2 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a};

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{4b};

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$-heteroarilo de 5 hasta 10 miembros substituidos con 0-2 R^{11b} y seleccionados de tiazolilo, oxazolilo, triazolilo, tetrazolilo, imidazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, benzimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, tetrahidroquinolinilo, y tetrahidroisoquinolinilo; y

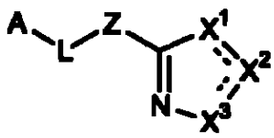
R^{11b} es, independientemente cada que se presenta, H, F, Cl, Br, CF_3, OMe, OEt, O(i-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, alquilo C_1-C_4-, Ph,

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o Bn;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos al cual están enlazados para formar un heterociclo 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g.

En un trigésimo segundo aspecto, la presente invención proporciona inter alia, un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (V):



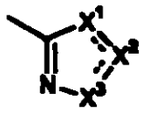
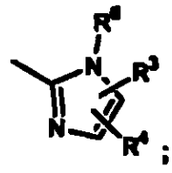
(V)

o sus estereoisómeros, tautómeros, sales, solvatos o profármacos del mismo farmacéuticamente aceptable, en donde:

A es carbociclo C_{3-10} substituido con 0-3 R^1 y 0-1 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^1 y 0-1 R^2;

X^1, X^2 y X^3 son independientemente CR^3, CR^4, CR^4CR^5, O, $S(O)_p$ N, NR^3, NR^6 o C(O); con la condición de que ningún enlace S-S, S-O, o O-O está presente en el anillo;

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con la condición de que  es diferente a  ;

Z es $-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-(CH_2)-$, $-NR^{13}-$, o $-NR^{13}CH_2-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)_pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, o $-C(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-NH$(alquilo C_{1-3}), $-N$(alquilo C_{1-3})$_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7C(O)OR^a$, $-CH_2NH_2$, $-CH_2NH$(alquilo C_{1-3}), $-CH_2N$(alquilo C_{1-3})$_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH$(alquilo C_{1-3}), $-CH_2CH_2N$(alquilo C_{1-3})$_2$, $-CH$(alquilo C_{1-4})NH_2, $-C$(alquilo C_{1-4})$_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-ciclopropilo, o alquilo C_{1-6} substituido con 0-1 R^{1a};

R^{1a} es H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR_8SO_2R^c$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^2 es, independientemente cada que se presenta, H, =O, F, CI, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, -

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$C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{2a}, alquenilo C_{2-6} substituido con 0-2 R^{2a}, alquinilo C_{2-6} substituido con 0-2 R^{2a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{2b}, o $-(CH_2)_r$ heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{2b};

R^{2a} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{2b} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, CF_3, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^C$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

alternativamente, cuando los grupos R^1 y R^2 son substituidos atomos del anillo adyacente, estos pueden tomarse juntos con los átomos en el anillo al cual se enlazan para formar un carbociclo o heterociclo de 5 hasta 7 miembros que comprende: átomos de carbono y 0-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el carbociclo o heterociclo es substituido con 0-2 R^{2b};

R^3 es, independientemente cada que se presenta, F, Cl, Br, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, SR^{3b}, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, -alquilo C_{1-4}-C(O), $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, alquilo C_{1-6} substituido por R^{3d}, alquenilo C_{2-6} substituido por R^{3d}, alquinilo C_{2-6} substituido por R^{3d}, cicloalquilo C_{3-6} substituido por 0-1 R^{3d}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

alternativamente, cuando dos grupos R^{3a} se localizan en átomos adyacentes, se toman junto con los átomos a los cuales se enlazan para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d}, o un heterociclo de 5 hasta 10 miembros que comprende:

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átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3d};

R^{3b} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3c} es, independientemente cada que se presenta, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$-carbocilo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3d} es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_pR^c$, $-(CF_2)_rCF^3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, alquinilo C_{2-6} substituido con 0-2 R^e, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con

0-3 R^d;

R^4 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{4b}, o $-(CH_2)_r$ heterociclo 5 de 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{4a} es, independientemente cada que se presenta, H, F, =O, alquilo C_{1-6}, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{4b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^C$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

alternativamente, cuando los grupos R^3 y R^4 se localizan en átomos adyacentes, pueden tomarse juntos para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el

heterociclo es substituido con 0-2 R^{3d};

R^5 es, independientemente cada que se presenta, H, F, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{5a}, alquenilo C_{2-6} substituido con 0-2 R^{5a}, alquinilo C_{2-6} substituido con 0-2 R^{5a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{5b}, o $-(CH_2)_r$ heterociclo 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{5b};

R^{5a} es, independientemente cada que se presenta, H, =O, OR^a, SR^a, F, Cl, Br, I, CF_3, OCF_3, CN, NO_2, $-NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{5b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^C$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^C$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, haloalquilo C_{1-4}, $-CH_2OR^a$, $-C(O)R^C$, $-C(O)_2R^C$, $-S(O)_2R^C$, o $-(CH_2)_r$ fenilo substituido con 0-3 R^d;

R^7 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n$-carbociclo C_{3-10}, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^C$, -CHO, $-C(O)_2R^C$, $-S(O)_2R^C$, $-CONR^8R^C$, -

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$OCONHR^c$, $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(arilo C_{6-10}); en donde el alquilo, carbociclo, heteroarilo, y arilo son opcionalmente substituidos con 0-2 R^f;

R^8 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo, o $-(CH_2)_n-$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde el alquilo, fenilo y heterociclo son opcionalmente substituidos con 0-2 R^f;

alternativamente, cuando R^7 y R^8, se enlazan al mismo nitrógeno, se combinan para formar un anillo heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d;

R^{8a} es, independientemente cada que se presenta, H, OH, alquilo C_{1-6}, alcoxi C_{1-4}, (arilo C_{6-10})-alcoxi C_{1-4}, $-(CH_2)_n-$fenilo, $-(CH_2)_n-$(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(arilo C_{6-10}); en donde el fenilo, arilo, y heteroarilo es opcionalmente substituido con 0-2 R^f;

R^9 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo; en donde el alquilo y fenilo son opcionalmente substituidos con 0-2 R^f;

R^{9a} es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

alternativamente, cuando R^8 y R^9, se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3R^{10a}, alquenilo C_{2-6} substituido con 0-3 R^{10a}, alquinilo C_{2-6} substituido con 0-3 R^{10a}, $-(CH_2)_r-$carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^{10a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c-$, $-S(O)R^c$, o $-S(O)_2R^c$;

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CR^{14}R^{15})_r-$carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CR^{14}R^{15})_r-$heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b};

R^{11a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, CF_3, SR^a, F, CN, NO_2, NR^7R^8, $-C(O)NR^7R^8$, -

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$NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^c$, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituidos con 0-3 R^d;

R^{11b} es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales se enlazan para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g;

R^{12} es, independientemente cada que se presenta, H, F, o alquilo C_{1-4};

R^{13} es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n$-fenilo, $-(CH_2)_n$-(heteroarilo de 5-10

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miembros), $-C(O)R^c$, $-C(O)OR^c$, $-CONR^aR^c$, $-OCONR^aR^c$, $-S(O)_2R^c$, $-C(O)O-$(alquilo C_{1-4})$-OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$-OC(O)-$(arilo C_{6-10}); en donde el alquilo, fenilo, heteroarilo, arilo son opcionalmente substituidos con 0-2 R^f;

R^{14} y R^{15} son, independientemente cada que se presentan, H, F, o alquilo C_{1-4};

alternativamente, R^{14} se combina con R^{15} para formar =O;

R^a es, independientemente cada que se presenta, H, CF_3, alquilo C_{1-6}, $-(CH_2)_r$-cicloalquilo C_{3-7}, $-(CH_2)_r$-arilo C_{6-10}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los grupos cicloalquilo, arilo y heteroarilo son opcionalmente substituidos con 0-2 R^f.

R^b es, independientemente cada que se presenta, CF_3, OH, alcoxi C_{1-4}, alquilo C_{1-6}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^c es, independientemente cada que se presenta, CF_3, alquilo C_{1-6} substituido con 0-2 R^f, cicloalquilo C_{3-6} substituido con 0-2 R^f, arilo C_{6-10}, heteroarilo de 5 hasta 10 miembros, (arilo C_{6-10})-alquilo C_{1-4}, o (heteroarilo de 5 hasta 10 miembros)-alquilo C_{1-4}, en donde los grupos arilo y heteroarilo son opcionalmente substituidos con 0-3 R^f;

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R^d es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, o alquinilo C_{2-6} substituido con 0-2 R^e;

R^e es, independientemente cada que se presenta, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^f es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-alquilo C_{1-4}, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, o $-(CH_2)_n$-fenilo;

R^g es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

n, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4;

p, cada que se presenta, se selecciona de 0, 1, y 2;

r, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4; y

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s, cada que se presenta, se selecciona de 1, 2, 3, y 4.

En un trigésimo tercer aspecto, la presente invención proporciona un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (V), dentro del alcance del trigésimo segundo aspecto en donde:

A es cicloalquilo C_{3-8} substituido con 0-1 R^1 y 0-3 R^2, cicloalquenilo C_{4-8} substituido con 0-1 R^1 y 0-3 R^2, fenilo substituido con 0-1 R^1 y 0-3 R^2, naftilo substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-1 R^1 y 0-3 R^2;

Z es $-C(R^{11})(R^{12})-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, o $-NR^{10}C(O)CH_2-$;

R^3 es, independientemente cada que se presenta, F, Cl, Br, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-cicloalquilo C_{3-8} substituido con 0-2 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está

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substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{4b};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{11b}.

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En un trigésimo cuarto aspecto, la presente invención proporciona un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (V), dentro del alcance del trigésimo segundo aspecto en donde:

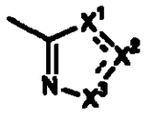
A es cicloalquilo C_{5-6} substituido con 0-1 R^1 y 0-2 R^2, cicloalquenilo C_{5-6} substituido con 0-1 R^1 y 0-2 R^2,, fenilo substituido con 0-1 R^1 y 0-3 R^2, naftilo substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-1 R^1 y 0-3 R^2;

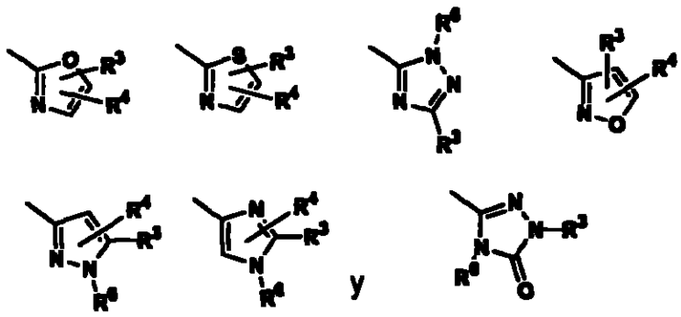
R^3 es, independientemente cada que se presenta, F, Cl, Br, $-(CH_2)_r-C(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3a} y 0-1 R^{3d}; y

R^6 es, independientemente cada que se presenta, H o alquilo C_{1-6}.

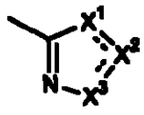
En un trigésimo quinto aspecto, la presente invención proporciona un método para tratar un trastorno tromboembólico

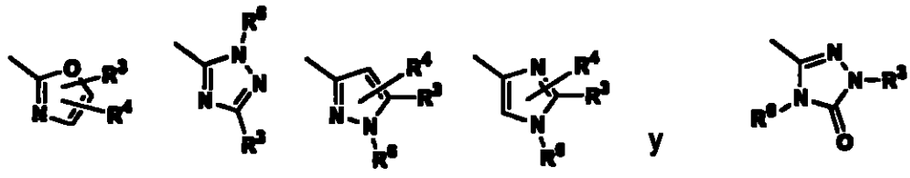
o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (V), dentro del alcance del trigésimo segundo aspecto en donde:

el grupo  es seleccionado de:



En un trigésimo sexto aspecto, la presente invención proporciona un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (V), dentro del alcance del trigésimo segundo aspecto en donde:

el grupo  es seleccionado de:

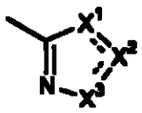


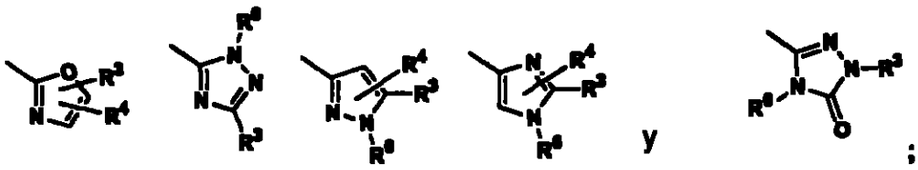
En un trigésimo séptimo aspecto, la presente invención

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proporciona un método para tratar un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (III), dentro del alcance del trigésimo segundo aspecto en donde:

A es substituido con 0-1 R^1 y 0-2 R^2 y se selecciona de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

el grupo  es seleccionado de:

 y ;

Z es $-CH(R^{12})-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, o $-NR^{10}C(O)CH_2-$;

R^3 es, independientemente cada que se presenta, F, Cl, Br, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido

con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d} o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^{4b};

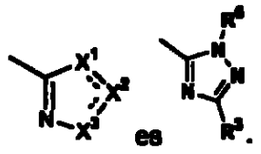
R^6 es H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^d; y

R^{12} es, independientemente cada que se presenta, H, F, o Me.

En otro aspecto, la presente invención proporciona un método para el tratamiento de un trastorno tromboembólico o inflamatorio, que comprende: administrar a un paciente en

necesidad del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la Fórmula (III), dentro del alcance del vigésimo octavo aspecto en donde:

el grupo  es .

En otro aspecto, L es $-C(O)NR^{10}-$ o $-NR^{10}C(O)-$.

En otro aspecto, L es $-C(O)NR^{10}-$.

En otro aspecto, L es $-NR^{10}C(O)-$.

En otro aspecto, L es $-C(O)NH-$ o $-NHC(O)-$.

En otro aspecto, L es $-C(O)NH-$.

En otro aspecto, L es $-NHC(O)-$.

En otro aspecto, la presente invención proporciona un compuesto seleccionado de los ejemplos o estereoisómeros, tautómeros, ejemplificados, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos.

En otra modalidad, la presente invención proporciona una composición farmacéutica novedosa, que comprende: un portador farmacéuticamente aceptable y una cantidad terapéuticamente efectiva de un compuesto de la presente invención o un estereoisómero, tautómero, o una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

En otra modalidad, la presente invención proporciona un proceso novedoso para elaborar un compuesto de la presente invención o un estereoisómero, tautómero, o una sal, solvato

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o profármaco farmacéuticamente aceptable del mismo.

En otra modalidad, la presente invención proporciona un proceso intermediario novedoso para elaborar un compuesto de la presente invención o un estereoisómero, tautómero, o una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende además agentes terapéuticos adicionales seleccionados de abridores del canal de potasio, bloqueadores del canal de calcio, inhibidores del intercambio de hidrógeno de sodio, agentes antiarrítmicos, agentes antiateroscleroticos, anticoagulantes, agentes antitrombóticos, agentes protrombolíticos, antagonistas de fibrinogeno, diuréticos, agentes anti-hipertensivos, inhibidores de ATPasa, antagonistas del receptor mineralocorticoide, inhibidores de la fosfodiesterasa, agentes antidiabéticos, agentes antiinflamatorios, antioxidantes, moduladores de la angiogénesis, agentes antiosteoporosis, terapias de reemplazo de hormona, moduladores del receptor de la hormona, contraceptivos orales, agentes antiobesidad, antidepresivos, agentes antiansiedad, agentes antipsicóticos, agentes antiproliferativos, agentes antitumor, agentes de enfermedad de reflujo gastroesofagal y antiúlcera, agentes de la hormona de crecimiento y/o secretagogos de la hormona de crecimiento,

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miméticos de tiroides, agentes antiinfecciosos, agentes antivirales, agentes antibacteriales, agentes antihongos, agentes que reducen el colesterol/lípidos y terapias de perfil de lípidos, y agentes que imitan el pre-acondicionamiento isquémico y/o pérdida de función cardiaca, o una combinación de las mismas.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende además agentes terapéuticos adicionales seleccionados de un agente antiarrítmico, un agente anti-hipertensivo, un agente anticoagulante, un agente antiplaquetas, un agente inhibidor de la trombina, un agente trombolítico, un agente fibrinolítico, un bloqueador del canal de calcio, un agente que reduce el colesterol/lípidos o una combinación de los mismos.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende además agentes terapéuticos adicionales seleccionados de warfarina, heparina no fraccionada, heparina de bajo peso molecular, pentasacáridos sintéticos, hirudina, argatroban, aspirina, ibuprofen, naproxeno, sulindac, indometacina, mefenamato, dipiridamol, droxicam, diclofenaco, sulfinpirazona, piroxicam, ticlopidina, clopidogrel, tirofiban, eptifibatida, abciximab, melagatran, ximelagatran, disulfatohirudina, activador del plasminógeno del tejido, activador del

plasminógeno del tejido modificado, anistreplasa, urocinasa, y estreptocinasa, o una combinación de los mismos.

En una modalidad preferida, la presente invención proporciona una composición farmacéutica en donde el agente terapéutico adicional es un agente anti-hipertensivo seleccionado de inhibidores ACE, antagonistas del receptor AT-1, antagonistas del receptor ET, antagonistas del receptor ET/AII dobles, e inhibidores de vasopeptidasa, un agente antiarrítmico seleccionado de inhibidores IKur, o un agente antitrombótico seleccionado de anticoagulantes seleccionados de trombina, otros inhibidores del factor XIa, otros inhibidores de calicreína, inhibidores del factor VIIa e inhibidores del factor Xa, y agentes antiplaquetas seleccionados de bloqueadores GPIIb/IIIa, antagonistas $P2Y_1$ y $P2Y_{12}$, antagonistas del receptor de tromboxano, y aspirina o una combinación de los mismos.

En una modalidad preferida, la presente invención proporciona composiciones farmacéuticas en donde los agentes terapéuticos adicionales son un agente antiplaquetas o una combinación de los mismos.

En una modalidad preferida, la presente invención proporciona una composición farmacéutica, en donde el agente terapéutico adicional es el agente antiplaquetas clopidogrel.

En otra modalidad, la presente invención proporciona un método para la modulación de la cascada de coagulación y/o el

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sistema de activación por contacto que comprende administrar a un paciente que necesite de tal tratamiento una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la presente invención o un estereoisómero, tautómero, una sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

En otra modalidad, la presente invención proporciona un método novedoso para tratar trastornos tromboembólicos que comprende: administrar a un paciente que necesite de tal tratamiento una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la presente invención o un estereoisómero, tautómero, una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

En otra modalidad, la presente invención proporciona un método novedoso, en donde el trastorno tromboembólico se selecciona del grupo que consiste de trastornos tromboembólicos cardiovasculares arteriales, trastornos tromboembólicos cardiovasculares venosos, trastornos tromboembólicos cerebrovasculares arteriales, y trastornos tromboembólicos cerebrovasculares venosos.

En otra modalidad, la presente invención proporciona un método novedoso, en donde el trastorno tromboembólico se selecciona de angina inestable, un síndrome coronario agudo, fibrilación atrial, primer infarto al miocardio, infarto al miocardio recurrente, muerte isquémica repentina, ataque

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isquémico transitorio, apoplejía, ateroesclerosis, enfermedad arterial oclusiva periférica, trombosis venosa, trombosis de vena profunda, tromboflebitis, embolismo arterial, trombosis arterial coronaria, trombosis arterial cerebral, embolismo cerebral, embolismo de riñón, embolismo pulmonar, y trombosis que resulta de (a) válvulas prostéticas u otros implantes, (b) catéteres permanentes, (c) endoprótesis vasculares, (d) derivación cardiopulmonar, (e) hemodiálisis, y (f) otros procedimientos en los cuales la sangre se expone a una superficie artificial que promueve la trombosis.

En otra modalidad, la presente invención proporciona un método para tratar trastornos inflamatorios que comprenden: administrar a un paciente que necesite del tratamiento una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la presente invención o un estereoisómero, tautómero, una sal, solvato o profármaco farmacéuticamente aceptable de los mismos.

En otra modalidad, la presente invención proporciona un método, en donde el trastorno inflamatorio se selecciona del grupo que consiste de sepsis, síndrome de distensión respiratorio agudo, y síndrome de respuesta sistémica-inflamatoria.

En otra modalidad, la presente invención proporciona un método novedoso para tratar un paciente que necesite de un tratamiento para un trastorno tromboembólico, que comprende:

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administrar un compuesto de la presente invención o un estereoisómero, tautómero, una sal, solvato o profármaco, farmacéuticamente aceptable de los mismos, en una cantidad efectiva para tratar trastorno tromboembólico.

En otra modalidad, la presente invención proporciona un método para tratar un paciente que necesita de un tratamiento de un trastorno inflamatorio, que comprende: administrar un compuesto de la presente invención o un estereoisómero, tautómero, una sal, solvato o profármaco farmacéuticamente aceptable del mismo en una cantidad efectiva para tratar un trastorno inflamatorio.

En otra modalidad, la presente invención proporciona un artículo novedoso de fabricación, que comprende:

(a) un primer recipiente;

(b) una composición farmacéutica localizada dentro del primer recipiente, en donde la composición, comprende: un primer agente terapéutico, que comprende: un compuesto de la presente invención o un estereoisómero, tautómero, sal, solvato o profármaco farmacéuticamente aceptable de los mismos; y,

(c) una hoja de inserto de paquete que establece que la composición farmacéutica pueda ser usada para el tratamiento de un trastorno tromboembólico y/o inflamatorio.

En otra modalidad preferida, la presente invención proporciona un artículo novedoso de fabricación, que además

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comprende:

(d) un segundo recipiente;

en donde los componentes (a) y (b) están localizados dentro del segundo recipiente y el componente (c) está localizado dentro o fuera del segundo recipiente.

En otra modalidad, la presente invención proporciona un artículo novedoso de fabricación, que comprende:

(a) un primer recipiente;

(b) una composición farmacéutica localizada dentro del primer recipiente, en donde la composición, comprende: un primer agente terapéutico, que comprende: un compuesto de la presente invención o un estereoisómero, tautómero, una sal, solvato o profármaco farmacéuticamente aceptable de los mismos; y,

(c) una hoja de inserto de paquete que establece que la composición farmacéutica pueda ser usada en combinación con un segundo agente terapéutico para tratar un trastorno tromboembólico y/o inflamatorio.

En otra modalidad preferida, la presente invención proporciona un artículo novedoso de fabricación, que además comprende:

(d) un segundo recipiente;

en donde los componentes (a) y (b) están localizados dentro

del segundo recipiente y el componente (c) está localizado dentro o fuera del segundo recipiente.

En otra modalidad, la presente invención proporciona un método novedoso, que comprende: administrar un compuesto de la presente invención o un estereoisómero, tautómero, sal, solvato o profármaco farmacéuticamente aceptable del mismo en una cantidad efectiva para tratar un trastorno tromboembólico y/o inflamatorio.

En otra modalidad, la presente invención proporciona un compuesto de la presente invención o un estereoisómero, tautomero, una sal, solvato o profármaco farmacéuticamente aceptable del mismo, para usarse en la terapia.

En otra modalidad, la presente invención también proporciona del uso del compuesto de la presente invención o un estereoisómero, tautómero, una sal, solvato o profármaco farmacéuticamente aceptable del mismo, para la manufactura de un medicamento para el tratamiento de un trastorno tromboembólico y/o inflamatorio.

La presente invención puede ser personificada en otras formas específicas sin alejarse del espíritu o atributos esenciales de ésta. Esta invención abarca todas las combinaciones de aspectos preferidos de la invención señalados aquí. Se entiende que cualquiera y todas las modalidades de la presente invención pueden ser tomadas en conjunto con cualquier otra modalidad o modalidades para

describir más modalidades preferidas adicionales. También se entiende que cada elemento individual de las modalidades preferidas es su propia modalidad preferida independiente. Además, cualquier elemento de una modalidad está proyectado para ser combinado con cualquiera de todos los otros elementos para cualquier modalidad para describir una modalidad adicional.

DEFINICIONES

Los compuestos de esta invención pueden tener uno o más centros asimétricos. A menos de que se indique de otra manera, todas las formas quirales (enantiomérica y diastereomérica) y racémicas de los compuestos de la presente invención se incluyen en la presente invención. Muchos isómeros geométricos de olefinas, enlaces dobles C=N, y similares pueden presentarse en los compuestos, y tales isómeros estables se contemplan en la presente invención. En consecuencia, los compuestos presentes pueden aislarse en formas ópticamente activas o racémicas. Esto es también conocido en la técnica para preparar formas activas ópticamente, tales como por resolución de formas racémicas o por síntesis de materiales de partida activos ópticamente. Todas las formas racémicas, (enantiómericas y

diastereoméricas), quirales y todas las formas isoméricas geométricas de una estructura están proyectadas, a menos que la forma isomérica o de estequiometría específica se indique específicamente. Todos los tautómeros de compuestos descritos o mostrados también están considerados para ser parte de la presente invención.

Preferiblemente, el peso molecular de los compuestos de la presente invención es menor que alrededor de 500, 550, 600, 650, 700, 750, u 800 gramos por mol. Preferiblemente, el peso molecular es menor que alrededor de 800 gramos por mol. Más preferiblemente, el peso molecular es menor que alrededor de 750 gramos por mol. Aún más preferiblemente el peso molecular es menor que alrededor de 700 gramos por mol.

Como se usa aquí, el término "alquilo" o "alquileno" pretende incluir ambos grupos de hidrocarburos alifáticos saturados de cadena recta y ramificada que tienen el número especificado de átomos de carbono. Por ejemplo, "alquilo C_1-C_{10}" o "alquilo C_{1-10}" (o alquileno), está proyectado para incluir grupos alquilo C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, y C_{10}. Adicionalmente, por ejemplo, el "alquilo C_1-$_6$" denota alquilo que tiene de 1 a 6 átomos de carbono. Los grupos alquilo pueden ser substituidos o no substituidos de manera que uno o más de sus hidrógenos son reemplazados por otro grupo

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químico. Los ejemplos de alquilo incluyen, pero no se limitan a metilo (Me), etilo (Et), propilo, (por ejemplo n-propilo e isopropilo), butilo (por ejemplo, n-butilo, isobutilo, t-butilo), pentilo (por ejemplo, n-pentilo, isopentilo, neopentilo), y similares.

El "alquenilo" o "alquenileno" pretenden incluir cadenas de hidrocarburos ya sea de una configuración lineal o ramificada que tienen uno o más enlaces dobles carbono-carbono los cuales pueden ocurrir en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquenilo C_2-C_6" (o alquenileno), se proyecta para incluir los grupos alquenilo C_2, C_3, C_4, C_5, y C_6. Los ejemplos de alquenilo incluyen, pero no se limitan a etenilo, 1-propenilo, 2-propenilo, 2-butenilo, 3-butenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, 2-metil-2-propenilo, 4-metil-3-pentenilo, y similares.

El "alquinilo" o "alquinileno" están proyectados para incluir cadenas de hidrocarburo ya sea de una configuración linear o ramificada y tienen uno o más enlaces triples de carbono-carbono los cuales pueden ocurrir en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquinilo C_2-C_6" (o alquinileno), se proyecta para incluir grupos alquinilo C_2, C_3, C_4, C_5, y C_6; tales como etinilo, propinilo,

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butinilo, pentinilo, hexinilo y similares.

"Halo" o "halógeno" incluye flúor, cloro, bromo, y yodo. "Haloalquilo" se refiere a una cadena recta o ramificada, que tiene uno o más substituyentes de halógeno. Los grupos haloalquilo del ejemplo incluyen, pero no se limitan a, CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2C_5, y similares.

El término "alcoxi" o "alquiloxi" se refiere a un grupo alquilo-O-. "Alcoxi C_{1-6}" (o alquiloxi), se proyecta para incluir grupos alcoxi C_1, C_2, C_3, C_4, C_5, y C_6. Los ejemplos de alcoxi incluyen, pero no se limitan a metoxi, etoxi, propoxi (por ejemplo, n-propoxi e isopropoxi), y t-butoxi, y similares. Similarmente, "alquiltio" o "tioalcoxi" representan un grupo alquilo como se definió anteriormente con el número indicado de átomos de carbono anexado a través de un puente de azufre; por ejemplo metilo-S-, etilo-S-, y similares.

"Haloalcoxi" o "haloalquiloxi" representan un grupo haloalquilo como se define arriba con el número indicado de átomos de carbono se enlazan a través de un puente de oxígeno. Por ejemplo, "haloalcoxi C_{1-6}" se pretende que incluya los grupos haloalcoxi C_1, C_2, C_3, C_4, C_5 y C_6. Los ejemplos de haloalcoxi incluyen, pero no se limitan a, trifluorometoxi, 2,2,2-trifluoroetoxi, pentafluorotoxi, y

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similares. Similarmente, "haloalquiltio" o "tiohaloalcoxi" representan un grupo haloalquilo como se define arriba con el número indicado de átomos de carbono se enlazan a través de un puente de azufre; por ejemplo, trifluorometil-S-, pentafluoroetilo-S- y similares.

El término "cicloalquilo" se refiere a los grupos alquilo ciclizados, que incluyen sistemas de anillo mono-, bi- o poli-cíclico. El C_{3-7} cicloalquilo se pretende que incluya los grupos cicloalquilo C_3, C_4, C_5, C_6 y C_7. Los ejemplos de los grupos cicloalquilo incluyen, pero no se limitan a ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, norbornilo, y similares.

Como se usa aquí, "carbociclo" o "residuo carbocíclico" se pretende que signifique cualquier anillo monocíclico o bicíclico de 3, 4, 5, 6, ó 7 miembros estable o bicíclico o tricíclico de 7, 8, 9, 10, 11, 12 ó 13 miembros, cualquiera de los cuales puede ser saturado, parcialmente insaturado, insaturado o aromático. Ejemplos de los carbociclos incluyen, pero no se limitan a ciclopropilo, ciclobutilo, ciclobutenilo, ciclopentilo, ciclopentenilo, ciclohexilo, cicloheptenilo, cicloheptilo, cicloheptenilo, adamantilo, ciclooctilo, ciclooctenilo, ciclooctadienilo, [3.3.0]biciclooctano, [4.3.0]biciclononano,

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[4.4.0]biciclodecano, [2.2.2]biciclooctano, fluorenilo, fenilo, naftilo, indanilo, adamantilo, antracenilo, y tetrahidronaftilo (tetralino). Como se muestra arriba, los anillos en el puente también se incluyen en la definición del carbociclo (por ejemplo, [2.2.2]biciclooctano). Los carbociclos preferidos, a menos de que se especifique de otra manera son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo e indanilo. Cuando el término "carbociclo" se usa, pretende incluir "arilo". Un anillo puenteado ocurre cuando uno o más átomos de carbono enlazan dos átomos de carbono no adyacentes. Los puentes preferidos son uno o dos átomos de carbono. Esto se observa que un puente siempre convierte a un anillo monocíclico en un anillo tricíclico. Cuando un anillo se puentea, los substituyentes relacionados por el anillo también pueden presentarse en el puente.

Los grupos "arilo" se refieren a hidrocarburos aromáticos monocíclicos o policíclicos, incluyendo, por ejemplo, fenilo, naftilo, fenantranilo, y similares. Las porciones arilo son bien conocidas y se describen, por ejemplo, en Hawley's Condensed Chemical Dictionary (13 ed.), R.J. Lewis, ed., J. Wiley & Sons, Inc., New York (1997). Los grupos arilo pueden estar substituidos o no substituidos.

Como se usó aquí, el término "heterociclo" o "grupo

heterocíclico" se proyectó para significar un anillo monocíclico o bicíclico de 5, 6, ó 7 miembros estable o un anillo bicíclico o heterocíclico tricíclico de 7, 8, 9, 10, 11, 12, 13 ó 14 miembros el cual es saturado, parcialmente insaturado, o completamente insaturado, y el cual consiste de átomos de carbono y 1, 2, 3, ó 4 heteroátomos independientemente seleccionados de N, O y S; y que incluye cualquier grupo bicíclico en el cual cualquiera de los anillos heterocíclicos definidos arriba se fusionan a un anillo de benceno. Los heteroátomos de nitrógeno y azufre pueden opcionalmente ser oxidados (esto es, N→ O y $S(O)_p$). El átomo de nitrógeno puede ser substituido o no substituido (esto es, N o NR en donde R es H u otro substituyente, si se define). El anillo heterocíclico puede estar anexado a su grupo colgante en cualquier heteroátomo o átomo de carbono lo cual resulta en una estructura estable. Los anillos heterocíclicos descritos aquí pueden ser sustituidos en un átomo de carbono o en uno de nitrógeno si el compuesto que resulta es estable. Un átomo de nitrógeno en el heterociclo puede ser opcionalmente cuaternizado. Se prefiere que cuando el número total de átomos de S y O en el heterociclo excede de 1, entonces estos heteroátomos no están adyacentes uno del otro. Se prefiere que el número total de átomos de S y O en

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el heterociclo no sea más de 1. Cuando el término "heterociclo" se usa, está proyectado para incluir heteroarilo.

Los ejemplos de heterociclos incluyen, pero no están limitados a, acridinilo, azocinilo, benzimidazolilo, benzofuranilo, benzotiofuranilo, benzoxazolilo, benzoxazolinilo, benztiazolilo, benztriazolilo, benztetrazolilo, benzisoxazolilo, benzisotiazolilo, benzimidazolinilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 2H,6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofurano, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolenilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isatinoilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolopiridinilo, isoxazolilo, isoxazolopiridinilo, metilendioxifenilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxindolilo, pirimidinilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatinilo, fenoxazinilo, ftalazinilo, piperazinilo,

piperidinilo, piperidonilo, 4-piperidonilo, piperonilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazol, piridoimidazol, piridotiazol, piridinilo, pirimidinilo, pirrolidinilo, pirrolinilo, 2-pirrolidonilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, tiazolilo, tienilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo, y xantenilo. También se incluyen los anillos fusionados y los compuestos espiro que contienen, por ejemplo, los heterociclos de arriba.

Los heterociclos preferidos de 5 a 10 miembros incluyen, pero no están limitados a, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo, oxazolidinilo, tetrahidrofuranilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo, triazolilo,

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benzimidazolilo, 1H-indazolilo, benzofuranilo, benzotiofuranilo, benztetrazolilo, benzotriazolilo, benzisoxazolilo, benzoxazolilo, oxindolilo, benzoxazolinilo, benztiazolilo, benzisotiazolilo, isationilo, isoquinolinilo, octahidroisoquinolinilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, isoxazolopiridinilo, quinazolinilo, quinolinilo, isotiazolopiridinilo, tiazolopiridinilo, oxazolopiridinilo, imidazolopiridinilo, y pirazolopiridinilo.

Los heterociclos preferidos de 5 a 6 miembros incluyen, pero no están limitados a, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo, oxazolidinilo, tetrahidrofuranilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo, y triazolilo. También se incluyen los anillos fusionados y los compuestos espiro que contienen, por ejemplo, los heterociclos de arriba.

Como se usó aquí, el término "grupo heterocíclico aromático" o "heteroarilo" se proyecta para significar un hidrocarburo aromático monocíclico y policíclico que incluye por lo menos un miembro de anillo de heteroátomo tal como azufre, oxígeno, o nitrógeno. Los grupos de heteroarilo incluyen, sin limitación, piridinilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, furilo, quinolilo, isoquinolilo, tienilo, imidazolilo, tiazolilo, indolilo,

pirroilo, oxazolilo, benzofurilo, benzotienilo, benztiazolilo, isoxazolilo, pirazolilo, triazolilo, tetrazolilo, indazolilo, 1,2,4-tiadiazolilo, isotiazolilo, purinilo, carbazolilo, benzimidazolilo, indolinilo, benzodioxolanilo, benzodioxano, y los similares. Los grupos heteroarilo pueden ser sustituidos o no sustituidos. El átomo de nitrógeno puede ser substituido o no substituido (esto es, N o NR en donde R es H u otro substituyente, si se define). Los heteroátomos de nitrógeno y azufre se pueden oxidar opcionalmente (esto es, N → O y S(O)p). Se debe observar que el número total de átmos S y O en el heterociclo aromático no es mayor a 1. Los anillos puenteados también se incluyen en la definición del heterociclo. Una anillo puenteado se presenta cuando uno o más átomos (esto es, C, O, N o S) se unen a dos átomos de carbono o nitrógeno no adyacentes. Los puentes preferidos incluyen pero no se limitan a, un átomo de carbono, dos átomos de carbono, un átomo de nitrógeno, dos átomos de nitrógeno y un grupo carbono-nitrógeno. Se debe observar que un puente siempre convierte un anillo monocíclico en un anillo tricíclico. Cuando se puentea un anillo, los substituyentes mencionados en el anillo también pueden estar presentes en el puente.

El término "contraión" se usa para representar una especie cargada negativamente pequeña tal como cloruro, bromuro, hidróxido, acetato y sulfato.

Como se refiere en la presente, el término "substituido", significa que uno o más átomos de hidrógeno se reemplazan con un grupo no hidrogenado, con tal que las valencias se mantengan normales y que la substitución resulte en un compuesto estable. Cuando un substituyente es ceto (esto es, =O), entonces 2 hidrógenos en el átomo son reemplazados. Los substituyentes ceto no son presentados en porciones aromáticas. Cuando un sistema de anillo (por ejemplo, carbocíclico o heterocíclico) es tal para ser sustituido con un grupo carbonilo o un enlace doble, este es proyectado para que el grupo carbonilo o un enlace doble sea parte (esto es, dentro) del anillo.

Cuando se presenta cualquier variable (por ejemplo, R^{2b}, R^{8b}, etc.) más de una vez en cualquier constituyente o fórmula para un compuesto, su definición en cada ocurrencia es independiente de su definición en todas las otras ocurrencias. Así, por ejemplo, si un grupo se muestra para ser substituido con 0-3 R^{2b}, entonces el grupo puede opcionalmente ser sustituido con hasta tres grupos R^{2b} y R^{2b} en cada ocurrencia se selecciona independientemente de la definición de R^{2b}. También, las combinaciones de substituyentes y/o variables son permisibles solamente si las combinaciones resultan en compuestos estables.

Cuando un enlace para un substituyente se muestra a través de un enlace que conecta dos átomos en un anillo,

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entonces los substituyentes pueden ser enlazados a cualquier átomo en el anillo. Cuando un substituyente se enlista sin indicar el átomo por medio del cual el substituyente se enlaza al resto del compuesto de una fórmula dada, entonces tal substituyente puede ser enlazado por medio de cualquier átomo en el substituyente. Las combinaciones de substituyentes y/o variables son permisibles solamente si las combinaciones resultan en compuestos estables.

Cuando se usa un anillo con puntos, dentro de una estructura de anillo de 5 hasta 8 miembros, este indica que la estructura del anillo puede estar saturada, parcialmente saturada o insaturada.

Como se usa en la presente, el término "grupo protector" para aminas significa cualquier grupo conocido en el arte de la síntesis orgánica para la protección de grupos amina que es estable a un agente reductor de éster, una hidrazina disubstituida, R4-M y R7-M, un nucleófilo, un agente reductor de hidrazina, un activador, una base fuerte, una base de amina obstruida y un agente ciclizante. Tales grupos protectores amina que cumplen estos criterios incluyen aquellos enlistados en Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) y "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), la descripción de la cual se incorpora por ello para referencia. Los ejemplos de grupos

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protectores amina incluyen, pero no se limitan a, los siguientes: (Fmoc); (1) tipos de acilo tales como formilo, trifluoroacetilo, ftalilo, y p-toluensulfonilo; (2) tipos de carbamato aromático tal como benciloxicarbonilo (Cbz) y benciloxicarbonilos susbtituidos, 1-(p-bifenil)-1-metiletoxicarbonilo, y 9-fluorenilmetiloxicarbonilo (Fmoc); (3) tipos de carbamatos alifáticos tales como terc-butoxicarbonil(Boc), etoxicarbonilo, diisopropilmetoxicarbonilo, y aliloxicarbonilo; (4) tipos de carbamatos de alquilo cíclicos tales como ciclopentiloxicarbonilo y adamantiloxicarbonilo; (5) tipos de alquilo tales como trifenilmetilo y bencilo; (6) trialquilsilano tal como trimetilsilano; (7) tipos que contienen tiol tales como feniltiocarbonilo y ditiasuccinoilo; y (8) tipos de alquilo tales como trifenilmetilo, metilo, y bencilo; y tipos de alquilo substituidos tales como 2,2,2-tricloroetilo, 2-feniletilo, y t-butilo; y tipos de trialquilsilano tales como trimetilsilano.

La frase "farmacéuticamente aceptable" se emplea en la presente para referirse a aquellos compuestos, materiales, composiciones, y/o formas de dosificación que están, dentro del alcance de juicio médico sólido, apropiados para uso en contacto con los tejidos de humano existentes y animales sin toxicidad, irritación, respuesta alérgica, u otro problema o

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complicación excesiva, en proporción con una relación beneficio/riesgo razonable.

El término "sal farmacéuticamente aceptable" se refiere a sales de ácido o base de los compuestos aquí descritos. Ejemplos de sales farmacéuticamente aceptables incluyen, pero no se limitan a, sales de ácido mineral u orgánico de residuos básicos tales como aminas; sales orgánicas o alcalinas de residuos ácidos tales como ácidos carboxílicos; y similares. Las sales farmacéuticamente aceptables de los compuestos de la invención se pueden preparar al hacer reaccionar las formas de ácido o base libre de estos compuestos con una cantidad estequiométrica de la base o ácido apropiado en agua o en un solvente orgánico, o en una mezcla de los dos; generalmente, se prefieren medios no acuosos como éter, acetato de etilo, etanol, isopropanol o acetonitrilo. Las listas de las sales se encuentran en Remington's Pharmaceutical Sciences, Ed. 17, Mack Publishing Company, Easton, PA, 1985, p.1418, la descripción de la cual se incorpora en la presente como referencia en su totalidad. Ejemplos de sales farmacéuticamente aceptables incluyen, pero no están limitados a, sales de ácido mineral u orgánico de residuos básicos tales como aminas; sales orgánicas o alcalinas de residuos ácidos tales como ácidos carboxílicos;

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y similares. Las sales farmacéuticamente aceptables incluyen las sales no tóxicas convencionales o las sales de amonio cuaternario del compuesto precursor formado, por ejemplo, de ácidos inorgánicos u orgánicos no tóxicos. Tales sales no tóxicas convencionales incluyen aquellos derivados de ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico, y nítrico, y similares; y las sales preparadas de ácidos orgánicos tales como acético, propiónico, succínico, glicólico, esteárico, láctico, málico, tartárico, cítrico, ascórbico, pamóico, maléico, hidroximaléico, fenilacético, glutámico, benzoico, salicílico, sulfanílico, 2-acetoxibenzoico, fumárico, toluensulfónico, metansulfónico, etanodisulfónico, oxálico, e isetiónico, y los similares.

Además, los compuestos de la fórmula I pueden tener formas de profármaco. Cualquier compuesto que se convierta in vivo para proveer el agente bioactivo (esto es, un compuesto de la fórmula I) es un profármaco dentro del alcance y espíritu de la invención. Varias formas de profármacos son bien conocidas en la técnica. Por ejemplo de los derivados de profármaco, ver:

a) Design of Prodrugs, editado por H. Bundgaard, (Elsevier, 1985), y Methods in Enzymology, Vol. 42, at pp.

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309-396, editado por K. Widder, y colaboradores, (Academic 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, en pp. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, Vol. 8, p. 1-38 (1992);

d) H. Bundgaard, y colaboradores, Journal of Pharmaceutical Sciences, Vol. 77, p. 285 (1988); y

e) N. Kakeya, y colaboradores, Chem Phar Bull., Vol. 32, p. 692 (1984).

La preparación de profármacos es bien conocida en la técnica y se describe en, por ejemplo, Medicinal Chemistry: Principles and Practice, ed. F. D. King, The Royal Society of Chemistry, Cambridge, UK, 1994, que se incorpora en la presente para referencia en su totalidad.

Los compuestos radioetiquetados de la presente invención, esto es, en donde uno o mas de los átomos descritos se reemplazan por un isótopo radioactivo de tal átomo (por ejemplo, C reemplazado por ^{13}C o por ^{14}C; e isótopos de hidrógeno incluyen tritio y deuterio), también se proporcionan en la presente. Tales compuestos tienen una variedad de usos potenciales como por ejemplo, estándares y

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reactivos para determinar la capacidad de un farmacéutico potencial para unirse a proteínas objetivo o receptores, o para compuestos que forman imágenes de esta invención enlazados a receptores biológicos in vivo o in vitro.

Los compuestos de la presente invención son, subsecuentemente a su preparación, preferiblemente aislados y purificados para obtener una composición que contiene una cantidad en peso igual o mayor del 98%, preferiblemente 99% del compuesto de la presente invención ("substancialmente puro"), el cual luego se usa o formula como se describió aquí. Los compuestos "substancialmente puros" también están contemplados aquí como parte de la presente invención.

"Compuesto estable" y "estructura estable" tienen la intención de indicar un compuesto que es suficientemente robusto para sobrevivir al aislamiento a un grado útil de pureza de una mezcla de reacción, y formulación en un agente terapéutico eficaz. Se prefiere que los compuestos de la presente invención no contengan un grupo N-halo, $S(O)_2H$, o S(O)H.

Además debe entenderse que los solvatos (por ejemplo, hidratos) de los compuestos de la presente invención también están dentro del alcance de la presente invención. Los

métodos de solvatación generalmente son conocidos en la técnica.

Como se usa en la presente, "tratar" o "tratamiento" cubre el tratamiento de un estado de enfermedad en un mamífero, particularmente en un humano, e incluye: (a) evitar que suceda un estado de enfermedad en un mamífero, en particular, cuando el mamífero se predispone al estado de enfermedad pero todavía no ha sido diagnosticado como que lo tiene; (b) inhibición del estado de enfermedad, esto es, suspender este desarrollo; y/o (c) aliviar el estado de enfermedad, esto es, provocando regresión del estado de enfermedad.

"Cantidad terapéuticamente efectiva" pretende incluir una cantidad de un compuesto de la presente invención que es efectivo cuando se administra solo o en combinación para inhibir el factor XIa y/o calicreína de plasma. "Cantidad terapéuticamente efectiva" también está proyectado para incluir una cantidad de la combinación de los compuestos reivindicados que es efectiva para inhibir el factor XIa y/o la calicreína de plasma. La combinación de los compuestos preferiblemente es una combinación sinérgica. La sinergia, como se describió, por ejemplo, por Chou and Talalay, Adv. Enzyme Regul. 1984, 22:27-55 ocurre cuando el efecto (en este caso, inhibición del factor XIa y/o calicreína de plasma) de

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los compuestos cuando se administra en combinación es mayor que el efecto aditivo de los compuestos cuando se administran solos como un agente simple. En general, un efecto sinérgico se demuestra más claramente en concentraciones sub-óptimas de los compuestos. La sinergia puede ser en términos de menor citotoxicidad, efecto antitrombótico incrementado, y/o efecto antiinflamatorio, o algún otro efecto benéfico de la combinación comparada con los componentes individuales.

La presente invención incluye además composiciones que comprenden uno o más compuestos de la presente invención y un portador farmacéuticamente aceptable. Un "portador farmacéuticamente aceptable" se refiere a un medio generalmente aceptado en la técnica para la administración de agentes biológicamente activos a animales en particular mamíferos. Los portadores farmacéuticamente aceptables se formulan de conformidad con un número de factores bien dentro de la visión de aquellos de experiencia ordinaria en la técnica. Estos incluyen, sin limitación: el tipo y naturaleza del agente activo de formularse; el sujeto al cual se le administrará la composición que contiene el agente, la vía pretendida de administración de la composición; y, la indicación terapéutica a dirigirse. Los portadores farmacéuticamente aceptables incluyen un medio líquido tanto acuoso como no acuoso así como una variedad de formas de

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dosis sólidas y semi sólidas. Tales portadores pueden incluir un número de diferentes ingredientes y aditivos además del agente activo, tales ingredientes adicionales se incluyen en la formulación por una variedad de razones, por ejemplo, estabilización del agente activo, aglutinantes, etc., bien conocidas por aquellas de experiencia ordinaria en la técnica. Las descripciones de portadores farmacéuticamente aceptables apropiados y factores involucrados en su selección se encuentran en una variedad de fuentes ya disponibles tales como por ejemplo, Remington Pharmaceutical Sciencies, 17th ed., Mack Publishing Company, Easton, PA, 1985, que se incorpora en la presente para referencia en su totalidad.

Síntesis

Los compuestos de la presente invención pueden ser preparados en un número de formas conocidas por un experto en la técnica de síntesis orgánica. Los compuestos de la presente invención pueden ser sintetizados usando los métodos descritos abajo, junto con métodos sintéticos conocidos en la técnica de química orgánica sintética, o por variaciones en ellas como se aprecia por aquellos expertos en la técnica. Los métodos preferidos incluyen, pero no están limitados a, aquellos descritos a continuación. Las reacciones se realizan en un solvente apropiado para los reactivos y materiales

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empleados y apropiados para las transformaciones que se efectúan. Se entenderá por aquellos expertos en la técnica de síntesis orgánica que la funcionalidad presente en la molécula debe ser consistente con las transformaciones propuestas. Algunas veces esto requerirá una evaluación para modificar el orden de los pasos sintéticos o para seleccionar un esquema de proceso particular sobre otro con el propósito de obtener un compuesto deseado de la invención. También, en la descripción de los métodos sintéticos descritos a continuación, se entenderá que todas las condiciones de reacción propuestas, incluyendo la elección del solvente, atmósfera de reacción, temperatura de reacción, duración del experimento y procedimientos de preparación, se eligen para ser las condiciones estándar para esa reacción, que se deben reconocer fácilmente por alguien experto en la técnica. Se entiende por alguien experto en la técnica de la síntesis orgánica, que la funcionalidad presente en diversas funciones de la molécula debe ser compatible con los reactivos y reacciones propuestas. Tales restricciones a los substituyentes que son compatibles con las condiciones de reacción serán fácilmente evidentes para alguien experto en la técnica y luego se deben usar métodos alternos.

También se reconocerá que otra consideración mayor en la planeación de cualquier ruta sintética en el campo es la elección juiciosa del grupo protector (PG) usado para la

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protección de los grupos funcionales reactivos presentes en los compuestos descritos en esta invención. Una cuenta autorizada que describe las muchas alternativas a los practicantes entrenados es Greene and Wuts (Protective Groups In Organic Synthesis, Wiley-Interscience, 3rd Edition, 1999).

Todas las referencias citadas en la presente se incorporan por ello en su totalidad en la presente para referencia.

Los compuestos de imidazol útiles para la síntesis de los compuestos de esta invención pueden sintetizarse de conformidad con el método general resumido en el Esquema de reacción 1 (Con tour-Gacera et al. Bioorg. Med. Chem. Lett. 2001, 11(5), 741-745). Un alfa aminoácido apropiadamente protegido o derivado [1; Y = R^{10}(PG)N- p Y = AC(O)N(R^{10})-] o derivado de ácido malónico [1; Y = alquil-OC(O)-] se disuelve en un solvente apropiado, tal como etanol/agua (1:1), y se trata con una base, tal como carbonato de cesio, para formar la sal de cesio. La sal se aísla y se vuelve a suspender en un solvente apropiado, tal como dimetil formamida, y se tombina con una alfa-bromocetona 2 para formar el ceto éster 3. Alternativamente, la formación del ceto éster 3 (X = arilo o heteroarilo) puede llevarse a cabo en un recipiente de reacción sencillo al formar la sal sal de cesio de 1 en el mismo solvente (por ejemplo, dimetil formamida) usado para la etapa de alquilación.

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El imidazol que tiene la estructura 4 se forma al calentar el ceto éster 3 hasta reflujo en un solvente apropiado, tal como xilenos, en presencia de un exceso de acetato de amonio usando una trampa Dean-Stark para remover el agua. La formación del imidazol también puede llevarse a cabo al combinar el ceto éster 3 y acetato de amonio en un solvente apropiado, tal como xileno o etanol o una combinación de solventes tales como dimetilformamida y etanol (1:1), usando calentamiento de microondas. Cuando Y = $R^{10}(PG)N-$, el grupo protector en la amina se remueve en la preparación para la acilación de la amina, que se resume en el Esquema de reacción 18. Por ejemplo, cuando el grupo protector es una porción BOC, la amina se desprotege con ácido fuerte, tal como ácido trifluoroacético en un solvente apropiado, tal como diclorometano, para dar el compuesto 5, donde Y'= $R^{10}HN-$. Cuando Y = Alq-OCO-, el éster puede hidrolizarse al disolverlo en un solvente apropiado tal como metanol y tratar el éster con una base tal como hidróxido de sodio acuoso para dar el 5 donde Y = $-CO_2H$.

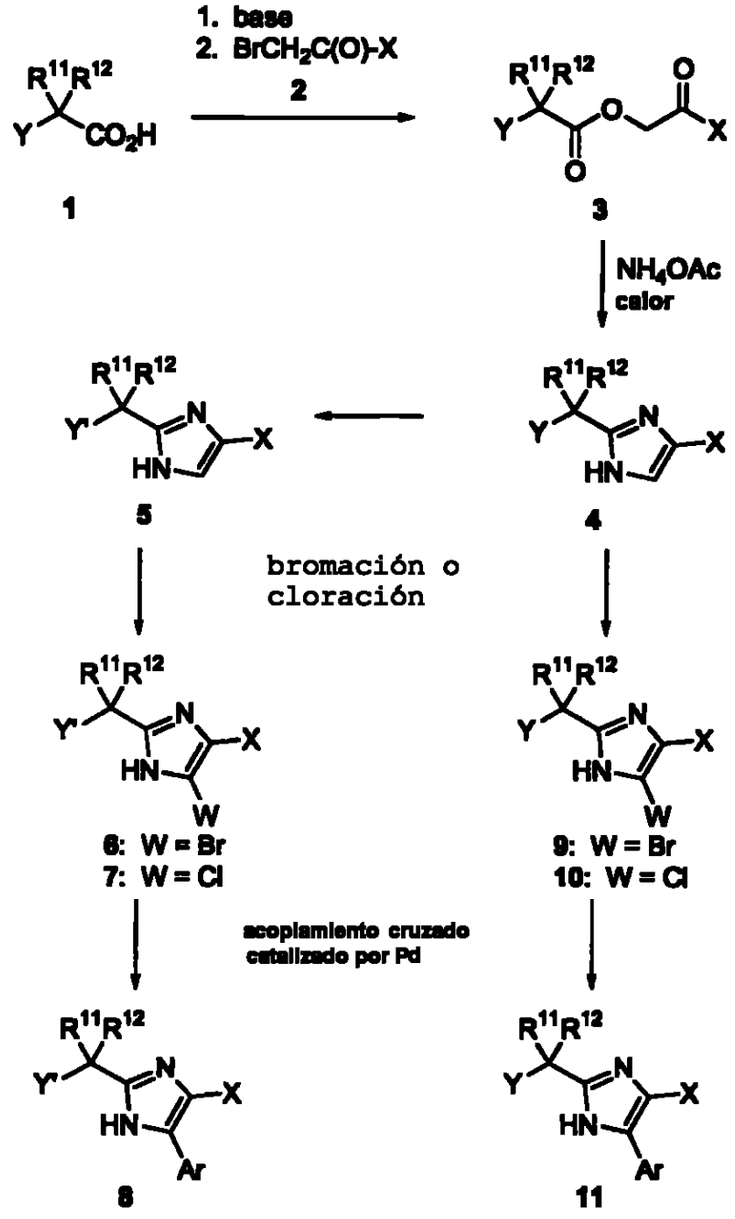
La incorporación de un grupo funcional adicional en el anillo de imidazol puede ralizarse por la bromación del carbono C-5 del anillo de imidazol usando, por ejemplo, bromo o N-bromosuccimida, en un solvente apropiado tal como cloruro de metileno o cloroformo para dar los compuestos 6 y 9. Alternativamente, el carbono C-5 puede clorarse con, por

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ejemplo, N-clorosuccinimida, usando un solvente apropiado tal como cloruro de metileno, acetonitrilo o cloroformo para dar los compuestos 7 y 10.

Los imidazoles bromados 6 y 9 proporcionan una funcionalidad apropiada para elaboración adicional usando una amplia variedad de procedimientos de acoplamiento cruzado catalizados por paladio conocidos por aquellos expertos en el arte, tales como aquellos descritos por Tsuji (Palladium Reagents and Catalyst: New Perspectives for the 21st Century, John Wiley & Sons, Ltd., 2004). A modo de ejemplo, la aplicación de un protocolo de acoplamiento Suzuki usando un método modificado de Zhong et al. (Org. Lett. 2004, 6, 929-931) y Bellina et al. (Synthesis 2004, 15, 2419-2440), donde los bromuros 6 ó 9 se combinan con ácido borónico en presencia de una base, típicamente fosfato tribásico o carbonato de sodio, y un catalizador de paladio, típicamente bis-(tri-t-butilfosfina)paladio(0), tris-(dibenciliden-acetona)paladio(0), o tetraquis-(trifenilfosfina)paladio(0), en un solvente apropiado, tal como tolueno 1,4-dioxano calentando hasta entre 80-110°C usando calentamiento convencional o de microondas, proporciona las estructuras 8 y 11, donde X = arilo o heteroarilo.

Esquema de reacción 1



Una síntesis alternativa del núcleo de imidazol se muestra en el Esquema de reacción 2. Un beta amino aldehído apropiadamente protegido 12, dihidrato glioxal trimérico 13 y

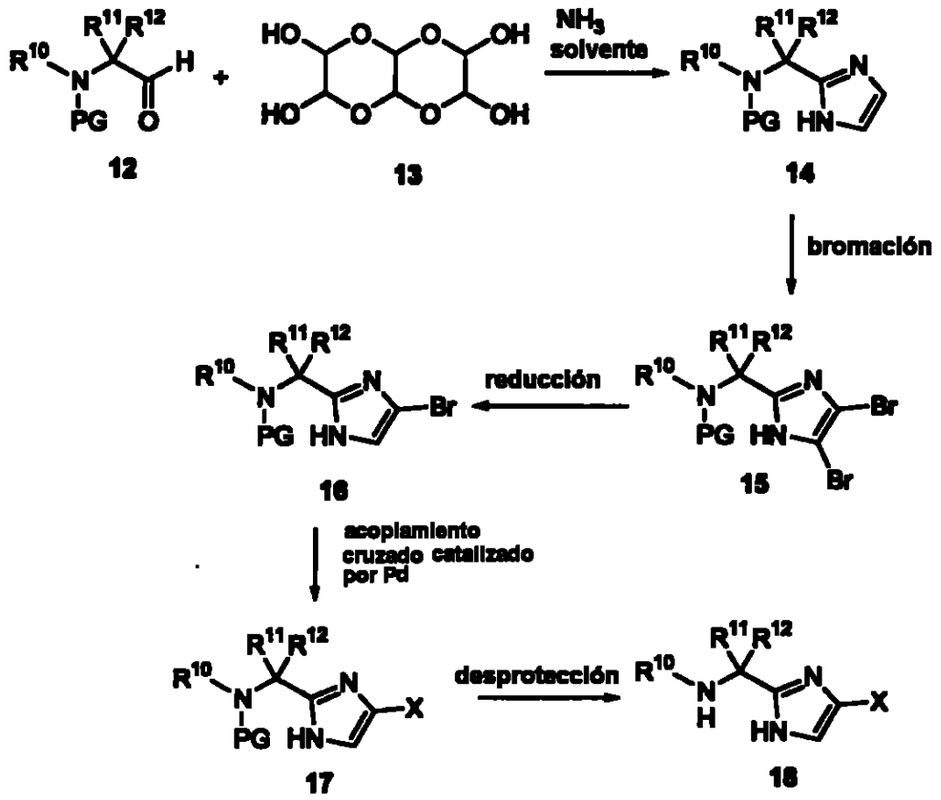
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amoniaco se combinan en un solvente apropiado tal como metanol y se agitan juntos a temperatura ambiente. El imidazol resultante 14 se disuelve en un solvente adecuado tal como cloroformo y se broma usando, por ejemplo, N-bromosuccinimida. Otros reactivos bromantes pueden emplearse, tal como bromo y otros solventes apropiados para condiciones de bromación, tales como cloruro de metileno o tetracloruro de carbono pueden usarse. El 4,5-dibromo imidazol 15 se trata con un agente reductor tal como sulfito ácido de sodio usando un sistema solvente bifásico que consiste de, por ejemplo, 1,4-dioxano y agua, y un catalizador de transferencia de fase tal como sulfato ácido de tetrabutilamonio. El monobromuro 16 de esta manera producido puede combinarse con un ácido aril borónico o ácido heteroaril boronico apropiadamente funcionalizado en un solvente apropiado tal como 1,4-dioxano o tolueno, y tratarse a temperatura elevada con una combinación de reactivo que consiste de, por ejemplo, dímero de bromuro de paladio(I)tri-terc-butilfosfina y fosfato tribásico de potasio de conformidad con un procedimiento modificado de Zhong et al. y Bellini et al. referenciado previamente. Otras combinaciones de reactivo que pueden utilizarse para el procedimiento de acoplamiento Suzuki son paladio tris-(dibenciliden-acetona)paladio(0), -tri-(terc-butil)-fosfonio tetra-fluoroborato, y fosfato tribásico de potasio. El grupo protector en la amina se remueve en la

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preparación para acilación de la amina que se resumen en el Esquema de reacción 17. Por ejemplo, cuando el grupo protector es una porción BOC, la amina se desprotege con un ácido fuerte, tal como ácido trifluoroacético, en un solvente apropiado tal como diclorometano, para dar la amina 18 como la sal bis-TFA.

Esquema de reacción 2

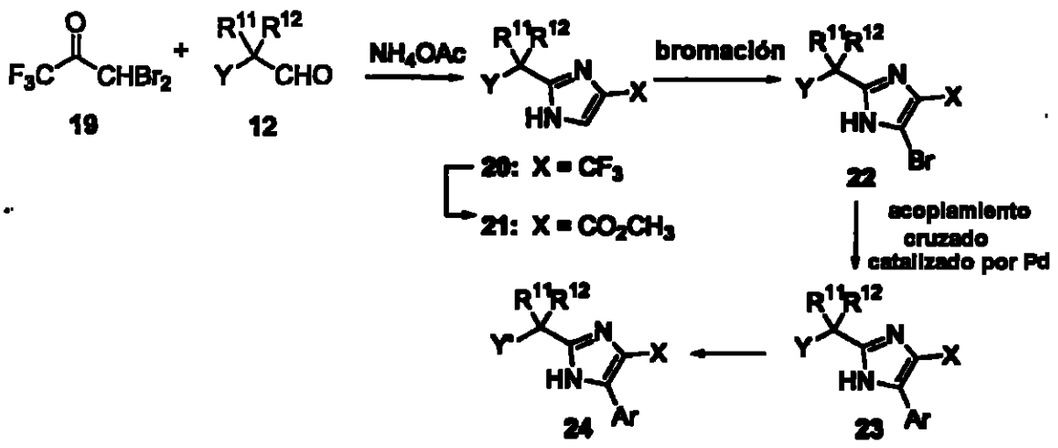


Otro método alternativo para la síntesis del anillo de imidazol se muestra en el Esquema de reacción 3. La 3,3-dibromo-1,1,1-trifluoropropan-2-ona (19) se combina con

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acetato de amonio con un solvente apropiado tal como agua y se calienta a 90°C, seguido por la adición de un aldehído 12 apropiadamente protegido. El trifluorometil imidazol de esta manera producido proporciona un intermediario para la síntesis de los análogos de C-5 trifluorometilo ilustrados por el compuesto 24, donde $X=CF_3$. Tales compuestos pueden accederse por métodos previamente ilustrados en los esquemas de reacción 1 y 2. Alternativamente, la porción trifluorometilo puede hidrolizarse bajo condiciones fuertemente básicas usando, por ejemplo metóxido de sodio, para proporcionar el orto éster que se hidroliza al éster de metilo 21, donde $X=-CO_2CH_3$. Este intermediario puede utilizarse usando procedimientos ya ilustrados en los Esquemas de reacción 1 y 2 para acceder a los compuestos tales como 24, donde $X=-CO_2CH_3$.

Esquema de reacción 3



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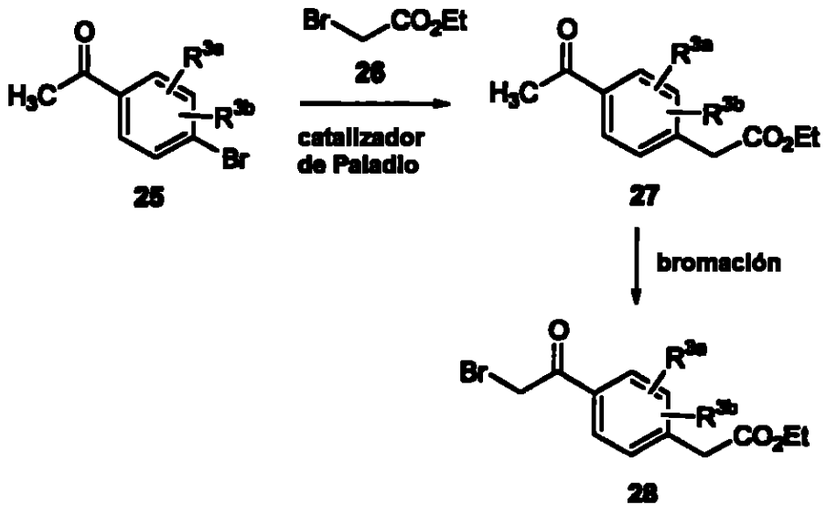
Los análogos de fenilalanina que portan substituyentes en el anillo fenilo que no están comercialmente disponibles se acceden fácilmente usando métodos conocidos por aquellos expertos en el arte. Para una revisión autorizada de los métodos para la síntesis de tales análogos que inician a partir de glicina, ver Maruka and Ooi (Chem. Rev. 2003, 103, 3013-3028).

Ciertos análogos de 2-bromoacetofenona que no están comercialmente disponibles pueden sintetizarse de materiales de partida comercialmente disponibles. Por ejemplo, el 2-(4-(2-bromoacetil)fenil)acetato de etilo (27: R^{3a}= R^{3b}= H) puede prepararse como se muestra en el Esquema de reacción 4. La 2,4'-dibromoacetofenona (25: R^{3a}= R^{3b}= H) y el bromoacetato de etilo (26) se disuelven en un solvente apropiado tal como tetrahidrofurano y se trata a temperatura elevada con una combinación de reactivos, tal como acetato de paladio (II), tris-(1-naftil)fosfina y fosfato tri-básico de potasio de conformidad con el método de Gossen et al. (Chem. Commun. 2001, 669-670). El intermediario, 2-(4-acetilfenil)acetato de etilo (27) se broma al disolverse en un solvente apropiado tal como cloroformo y se trata con un reactivo bromante tal como bromo para dar el 2-(4-(2-bromoacetil)fenil)acetato de etilo (28). Esta secuencia de reacción también puede emplarse para preparar los otros regioisómeros y análogos de 28 que contienen los grupos funcionales compatibles con la secuencia

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de reacción descrita.

Esquema de reacción 4



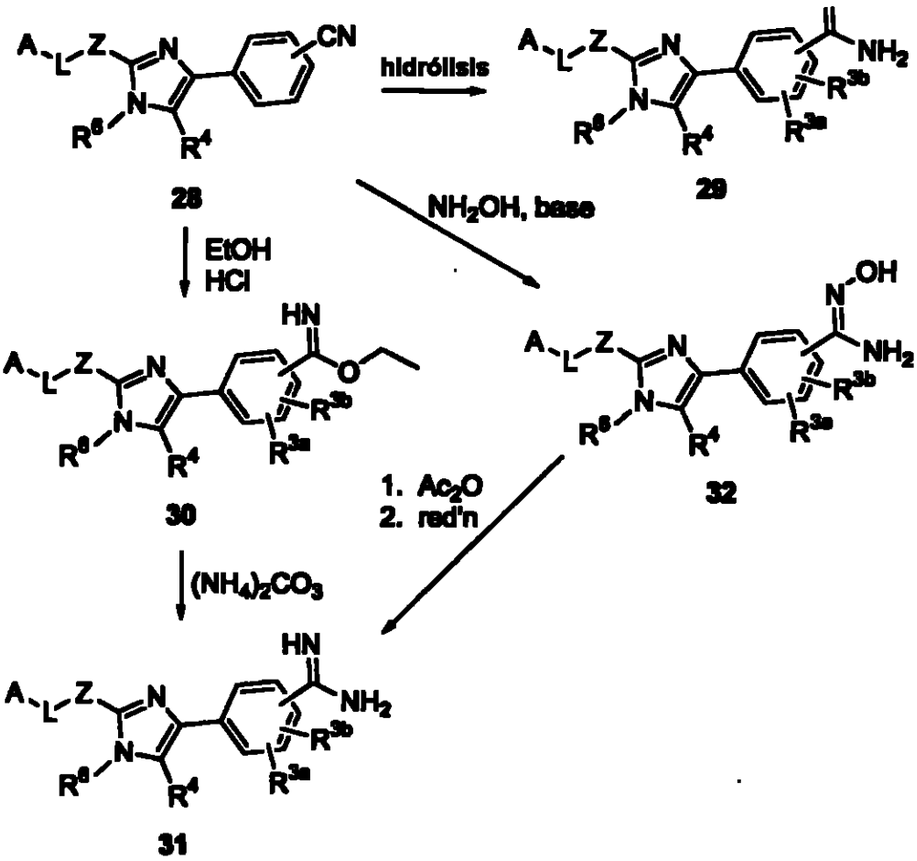
Ciertos grupos funcionales presentes en las estructuras finales deberán, en virtud de la compatibilidad con la formación de la imidazol mostrado en los Esquemas de reacción 1-3, incorporarse en la estructura después de que el anillo de imidazol se ha formado. Los ejemplos de tales grupos funcionales incluyen pero no se limitan a, carbamoilo, aminoindazolilo, aminobencisoxazolilo y aminoquinazolinoilo (ver Esquemas de reacción 5 y 6).

El grupo carbamoilo, ilustrado en la estructura 29 en el Esquema de reacción 5, puede incorporarse en la estructura final por la hidrólisis del nitrilo usando, por ejemplo, carbonato de potasio, peróxido de hidrógeno, y DMSO como solvente, de conformidad con el método de Katrizky et al.

400, 462

(Synthesis 1989, 12, 949-50). Cuando el nitrilo se localiza para al anillo de imidazol, deberá agregarse óxido de magnesio a la mezcla de reacción. El grupo amidina ilustrado en la estructura 31, puede incorporarse en la estructura final, por medio de la reacción Pinner seguido por amonolisis. Alternativamente, el nitrilo 28 puede combinarse con clorohidrato de hidroxilamina en presencia de una base, tal como trietilamina, para dar la amidoxina 32, que después de la acetilación con anhídrido acético se reduce por una variedad de métodos que incluyen pero no se limitan por, hidrogenación catalítica usando, por ejemplo, paladio en carbono e hidrógeno (Judkins et al. Syn Comm. 1996, 26, 4351-4367), o al usar en metal activo tal como zinc. A modo de ilustración, el grupo nitrilo precursor mostrado en la estructura 28 en el esquema 5 puede incorporarse en las estructuras intermediarias al usar, en reacciones separadas, 4-(2-bromo-acetil)-benzonitrilo, 3-(2-bromo-acetil)-benzonitrilo, o 2-(2-bromo-acetil)-benzonitrilo para el reactivo descrito como $BrCH_2C(O)X$ en el Esquema de reacción 1.

Esquema de reacción 5

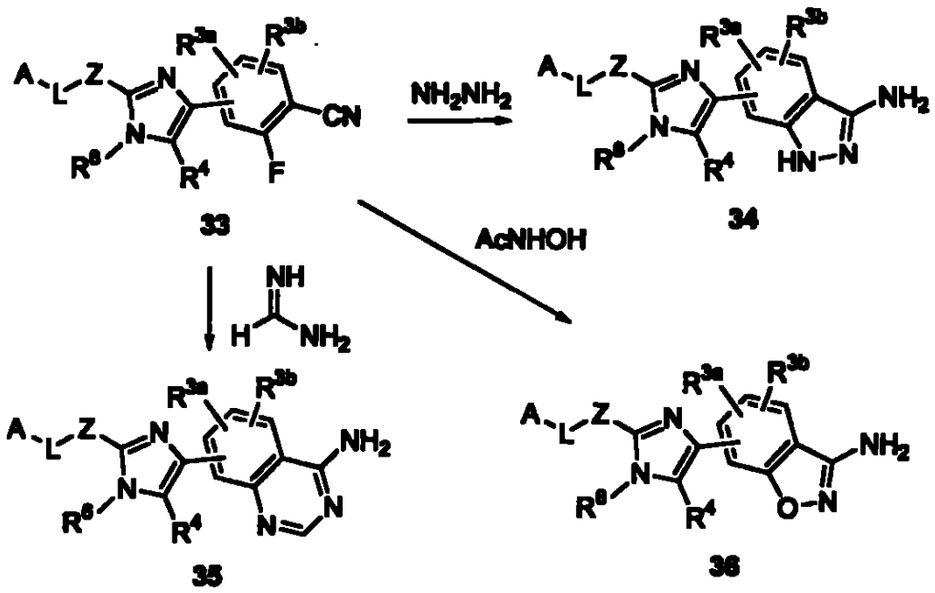


Los grupos funcionales aminoindazol, aminobencisoxazol y aminoquinazolina pueden incorporarse en la estructura final usando un intermediario común que contiene un anillo fenilo que porta un orto fluoro nitrilo como se muestra en la estructura 33 (Esquema de reacción 6). El grupo funcional amino-indazol (34) se produce, por ejemplo, al calentar un 33 con monohidrato de hidrazina en un solvente apropiado tal como N-butanol. El calentamiento puede darse convencionalmente o por medio de irradiación de microondas, y la temperatura requerida para la conversión del orto fluoro

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nitrilo al amino indazol depende de la relación regioisomérica entre el orto fluoro nitrilo y el anillo de imidazol. Típicamente, temperaturas de 160°C se requieren para la formación del amino indazol cuando el nitrilo se localiza para al anillo de imidazol. La aminoquinazolina (35) se produce al combinar el orto fluoro nitrilo (33) con acetato de formamidina, u otras formas de sal apropiadas en un solvente apropiado, tal como dimetil acetamida o dimetil formamida y calentando hasta aproximadamente 140°C. La conversión del orto fluoro nitrilo al aminobenzisoxazol (36) puede realizarse al combinar el fluoro nitrilo 33 con un ácido acetoxihidroxámico en presencia de una base tal como carbonato de potasio.

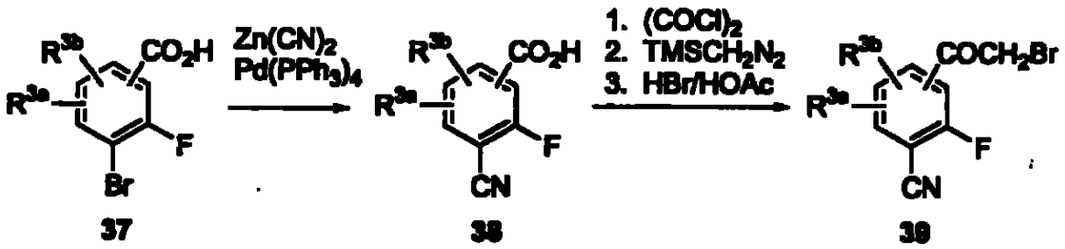
Esquema de reacción 6



463 465

Una síntesis general de las alfa bromocetonas que contienen un orto fluoro nitrilo se ilustra en el esquema de reacción 7. Un ácido bromo-fluoro-benzoico apropiadamente substituido (37) se convierte al nitrilo correspondiente 38 usando, por ejemplo, cianuro de zinc y tetraquis-(trifenilfosfina)paladio(0) en un solvente apropiado tal como dimetil formamida, y calentando hasta 90°C. El nitrilo 38 de esta manera producido se trata secuencialmente con cloruro de oxalilo en un solvente apropiado, tal como diclorometano, que contiene algunas gotas de DMF, luego se trata con trimetilsilildiazometano en un solvente apropiado o una combinación de solvente, tal como acetonitrilo y hexano. La diazocetona intermediaria se aísla y se trata con ácido bromhídrico y ácido acético para proporcionar la alfa bromocetona 39.

Esquema de reacción 7

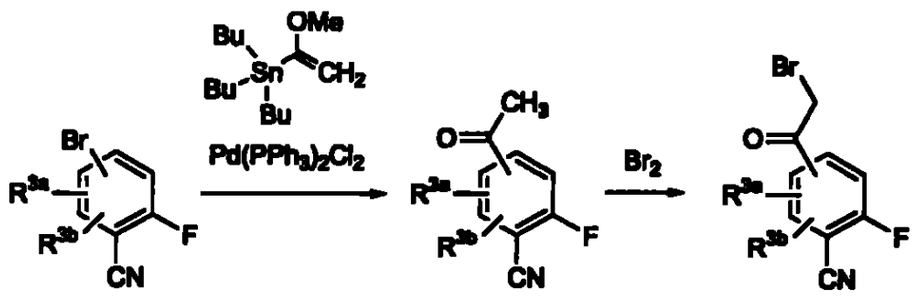


Alternativamente, la bromocetona 39 puede sintetizarse a partir de un orto fluoro nitrilo apropiadamente substituido

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que contiene un bromuro (40 Esquema de reacción 8) por el tratamiento secuencial con tributil-(1-metoxivinil)estanano y un catalizador de paladio, tal como bis-(trifenilfosfina)dicloro-paladio (II), en un solvente apropiado, tal como tolueno y calentando a reflujo, seguido por ácido clorhídrico acuoso, típicamente a una concentración del 5% (p/v). La metil cetona resultante 41 se combina con bromo en un solvente apropiado tal como cloroformo o cloruro de metileno, para producir la bromocetona 39. Las rutas sintéticas alternativas 39 diferentes a aquellas ilustradas en los Esquemas de reacción 7 y 8 pueden divisarse por alguien experto en el arte dependiendo de los regioisómeros comercialmente disponibles para posibles combinaciones de R^{3a} y R^{3b} contenidos en el anillo carbocíclico.

Esquema de reacción 8

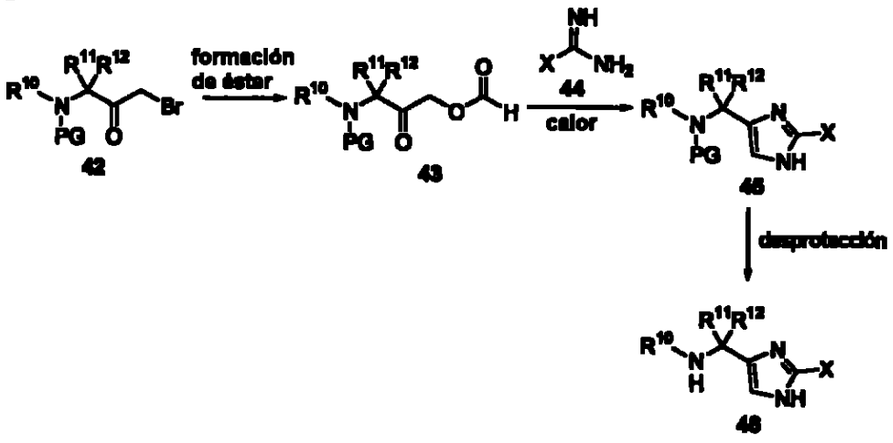


40 41 39

Una secuencia diferente de transformaciones químicas se proporciona para la síntesis de un segundo regioisómero de los imidazoles útiles en la preparación

de los compuestos de esta invención como se muestra en el Esquema de reacción 9. Una alfa-bromocetona 42 que contiene la substitución apropiada se combina con formiato de sodio en un solvente apropiado, tal como etanol y se calienta a reflujo. El ceto éster 43 formado de esta manera se disuelve en un solvente, por ejemplo, etanol, y se combina con una amidina apropiadamente substituida 44 (X = arilo o heteroarilo) en presencia de una base, por ejemplo, bicarbonato de sodio. El imidazol 45 de esta manera formado tiene la regio-configuración opuesta en comparación con los imidazoles ilustrados en los Esquemas de reacción 1-3. La remoción del grupo protector amina, PG, en la preparación para la acilación del grupo amino se lleva a cabo como se describe previamente para dar el amino imidazol 46.

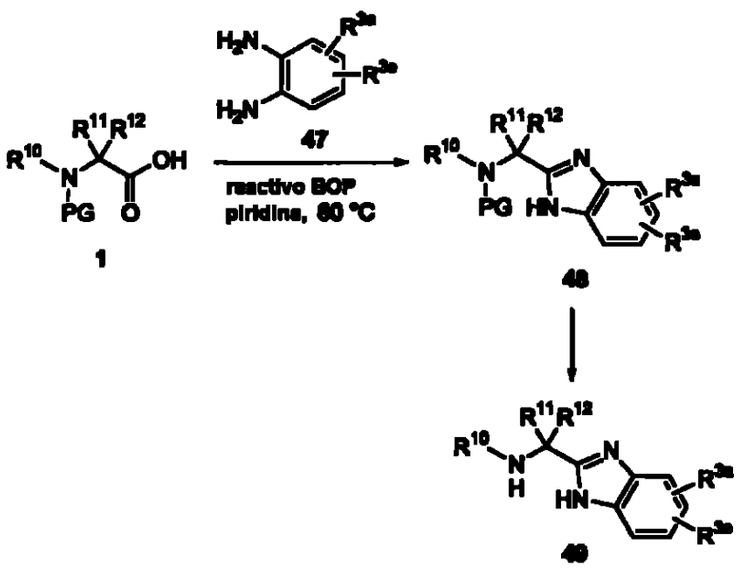
Esquema de reacción 9



Los compuestos de bencimidazol útiles para preparar

compuestos de esta invención pueden sintetizarse de conformidad con el procedimiento general mostrado en el Esquema de reacción 10. Un aminoácido apropiadamente protegido y una fenil diamina apropiadamente substituida 22 se disuelven en un solvente, por ejemplo, piridina y se trata con un reactivo que forma un enlace amida tal como el reactivo BOP. La mezcla de reacción se calienta hasta 80°C para efectuar el cerrado del anillo para el bencimidazol 23. El grupo protector en la amina se remueve como antes en la preparación para la acilación de la amina, como se resume abajo en el Esquema de reacción 17.

Esquema de reacción 10

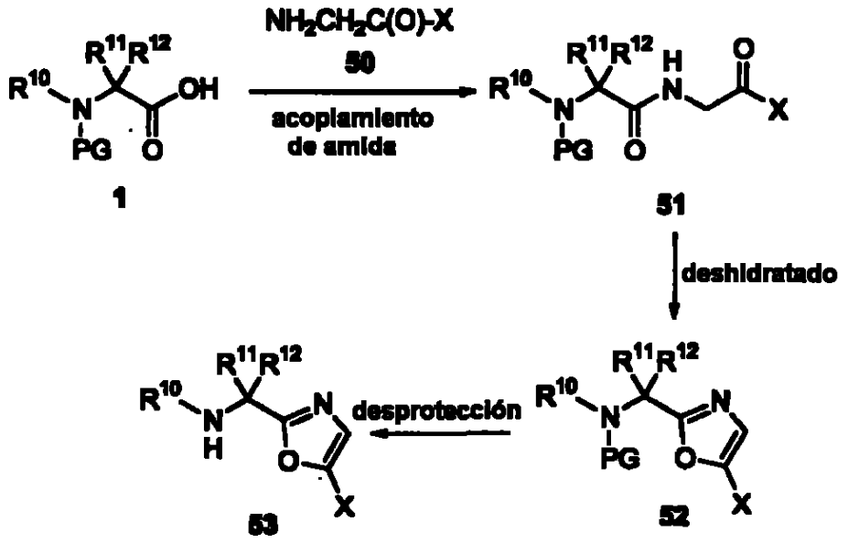


Un procedimiento general para la síntesis de oxazoles que tienen los substituyentes en las posiciones 2 y 4 útiles

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para la síntesis de los compuestos de esta invención se muestra en el Esquema de reacción 6. Un aminoácido apropiadamente protegido 1 y beta-ceto amina 50 (X = arilo o heteroarilo) se disuelven en un solvente apropiado, por ejemplo piridina, y se trata con un reactivo de acoplamiento amida, por ejemplo, reactivo BOP, a temperatura ambiente. La ceto amida 51 de esta manera formada se deshidrata al disolverse en un solvente apropiado tal como DMF y se trata la solución con oxicloruro de fósforo a temperatura elevada (Sow et al. J. Org. Chem. 1990, 55, 386). El oxazol 52 se desprotege en la preparación para la acilación de la amina 53, que se resume en el Esquema de reacción 17.

Esquema de reacción 11

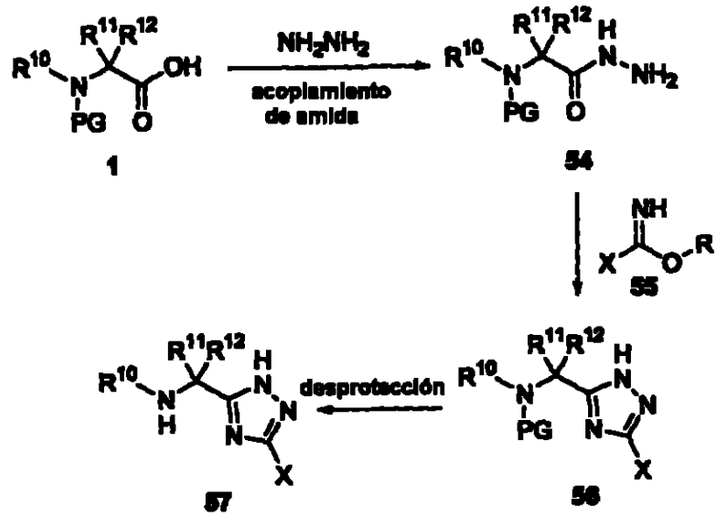


Los triazoles apropiadamente funcionalizados útiles para la síntesis de los compuestos de esta invención pueden

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sintetizarse de conformidad con el procedimiento resumido en el Esquema de reacción 12. Un aminoácido 1 apropiadamente protegido y la hidracina se disuelven en un solvente apropiado, tal como piridina y se trata con un enlace amida que forma un reactivo. El ácido hidrazoico resultante 54 se condensa con un imidato apropiadamente substituido 55 (X = arilo o heteroarilo). Cuando el imidato está en forma de sal de clorohidrato, la adición de una base tal como trietilamina se requiere. Los solventes tales como acetonitrilo pueden emplearse. El triazol 56 de esta manera formado, se desprotege para proporcionar la amida 57, que se usa en el Esquema de reacción 17 abajo. Por ejemplo, cuando el grupo protector es una porción BOC, la amina se desprotege con ácido trifluoroacético en diclorometano para dar la amina 53 como la sal bis-TFA.

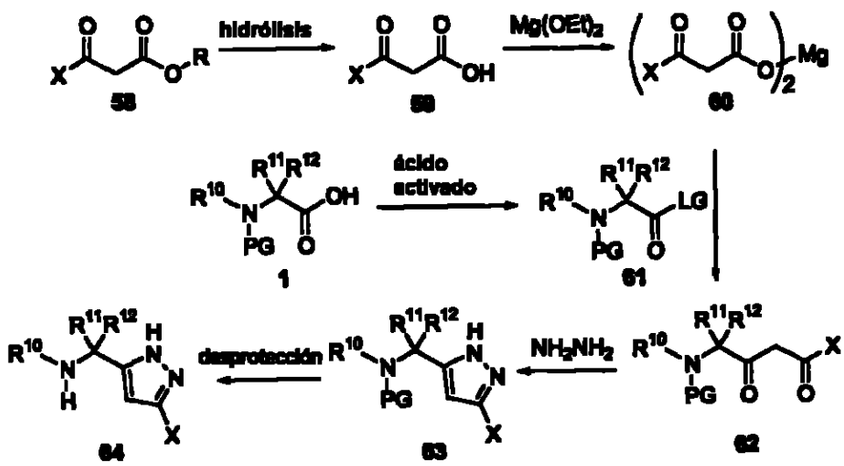
Esquema de reacción 12



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Los pirazoles apropiadamente substituidos útiles para la síntesis de los compuestos de esta invención pueden sintetizarse usando los procedimientos mostrados en el esquema de reacción 13 (Shunsaku Ohta et al. Chem. Pharm. Bull. 1981, 29(10), 2762). Un β-ceto éster apropiadamente substituido 58 (X = arilo o heteroarilo) se disuelve en un solvente apropiado y el éster se hidroliza con, por ejemplo, hidróxido de sodio. La sal de magnesio (60) del beta ceto ácido 59 se forma al disolver el ácido en un solvente apropiado tal como metanol y THF seguido por la adición de etóxido de magnesio. En una secuencia de reacción separada, el ácido carboxílico de un aminoácido apropiadamente protegido 1 (Y = $R^{10}N(PG)$-) se activa con, por ejemplo, carbonil diimidazol para dar el aminoácido activado 61 (LG = imidazol-1-ilo en esta ilustración). El compuesto 60 y 61 se combinan en un solvente apropiado, por ejemplo, DMF, para dar la beta dicetona 62. El tratamiento de 62 con hidrazina a temperaturas elevadas proporciona el pirazol 63. Cuando el grupo amino de 64 se protege con una porción CBz, el grupo protector puede removerse por hidrogenación catalítica usando, por ejemplo, paladio en carbono e hidrógeno elemental para dar la amina 64.

Esquema de reacción 13

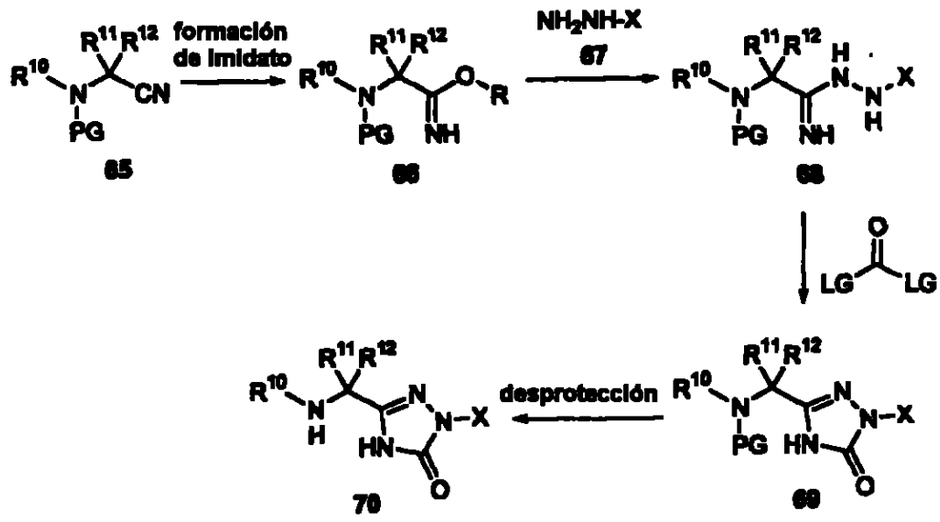


Un procedimiento general para la formación de triazolonas substituidas útiles para la síntesis de los compuestos de esta invención se muestra en el Esquema de reacción 14. Un beta-amino nitrilo apropiadamente substituido protegido 65 se trata con la sal de sodio de un alcohol, por ejemplo, metóxido de sodio, para formar el imidato 66. El imidato 66 se hace reaccionar con una hidrazina apropiadamente substituida 67 (X = arilo o heteroarilo) para formar la amino amidina 68 (Yanagisawa et al. J. Med. Chem. 1984, 27 (7), 849). El tratamiento de 68 con un carbonilo bis-activado tal como carbonil diimidazol (LG = imidazol-1-ilo) proporciona la triazolona 69. La desprotección del grupo amino 69 se lleva a cabo en la preparación para la acilación del nitrógeno, y se resumen en el Esquema de reacción 17. Por ejemplo, cuando la amina se protege con una porción CBz, el

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grupo protector puede removerse usando hidrogenación catalítica que usa, por ejemplo, paladio en carbón e hidrógeno o, alternativamente, por el tratamiento con HBr en HOAC o TFA puro para dar la amina 70.

Esquema de reacción 14

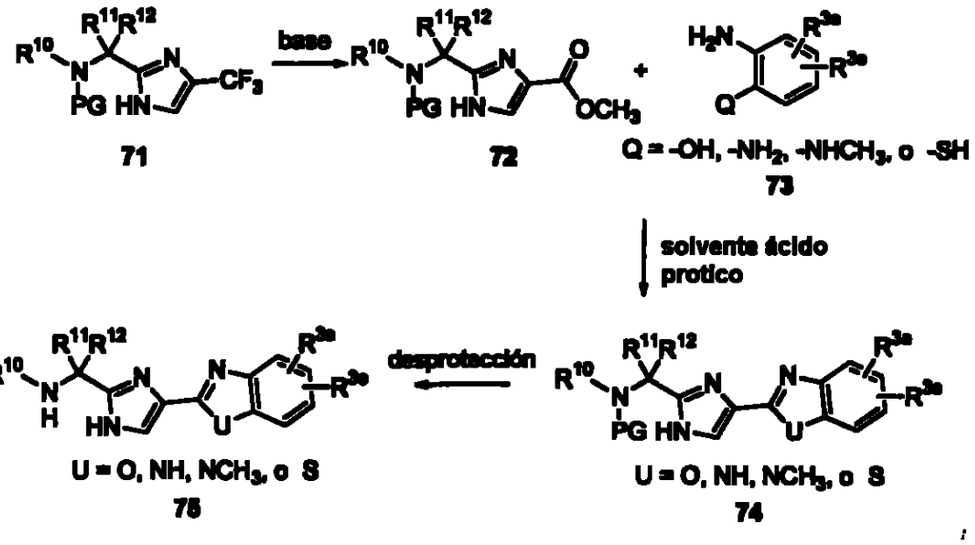


La síntesis de imidazoles substituidos con heterociclo de anillo fusionado en la posición 4 se muestra en el Esquema de reacción 15. Un 4-trifluorometil imidazol apropiadamente protegido y funcionalizado 71 está disponible de conformidad con la química resumida en el Esquema de reacción 3. El imidazol 71 se disuelve en un solvente apropiado tal como metanol y se calienta en presencia de una base tal como metóxido de sodio. El éster de metilo 72 de esta manera formado se disuelve en un solvente apropiado, por ejemplo, tetrahidrofurano, y se combina con una anilina 47 substituida en la posición orto con ya sea hidroxi, amino, mono alquil amino o tiol. La anilina empleada pueden tener

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substituyentes adicionales R^{3a} y R^{3e}, conocidos por aquellos expertos en el arte para ser compatibles con las condiciones de reacción. Los dos reactivos se tratan con un ácido prótico, por ejemplo, ácido para-toluen sulfónico, para efectuar la adición de la anilina y la posterior ciclización y deshidratación para forma el heterociclo fusionado 74. El grupo protector amina se remueve en la preparación para la acilación de la amina, la cual se resume en el Esquema de reacción 17. Cuando el grupo protegido es una porción BOC, la amina se desprotege con ácido fuerte tal como ácido trifluoroacético o HCl en un solvente apropiado tal como diclorometano o dioxano para dar la amina 75 como la sal bis-TFA.

Esquema de reacción 15

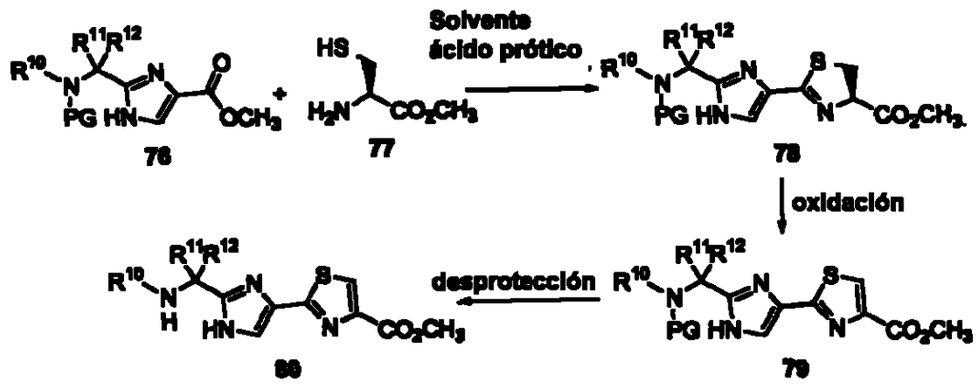


71 72 73 74 75

Los derivados de tiazol-2-il imidazol útiles para la síntesis de los compuestos de esta invención pueden

prepararse como se muestra en el Esquema de reacción 16. Un éster apropiadamente substituido 76 y un beta amino tiol tal como éster de metil cisteina 77 se combinan en un solvente apropiado tal como tetrahidrofurano y se trata con ácido protico tal como ácido camfor sulfónico. Otros beta amino tioles que tienen grupos funcionales compatibles con estas condiciones pueden emplearse en esta reacción. La tiazolidina resultante 78 se oxida al tiazol 79 usando, por ejemplo, dióxido de manganeso. Otros oxidantes apropiados pueden emplearse en esta etapa tales como 2,3-dicloro-5,6-diciano-1,4-benzoquinona. El grupo amino de 79 se desprotege en la preparación para la acilación. Por ejemplo, cuando el grupo protector es una porción BOC, la amina se desprotege con ácido fuerte tal como ácido trifluoroacético en un solvente apropiado tal como diclorometano para dar la amina 80 como la sal bis-TFA.

Esquema de reacción 16



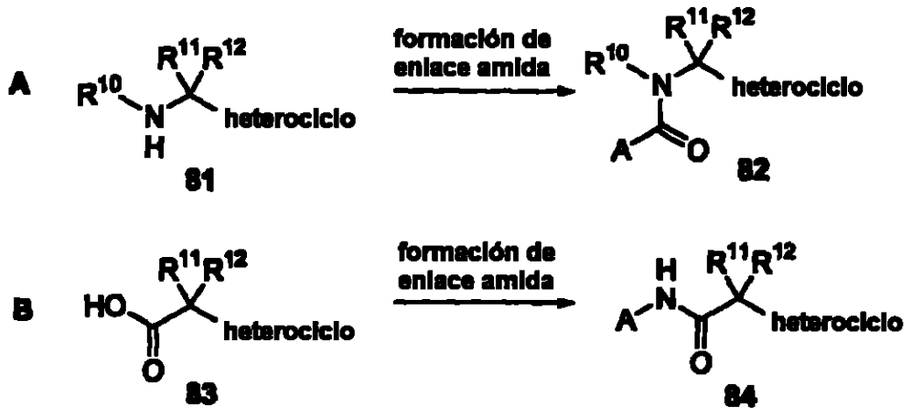
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Cada uno de los esquemas de reacción 1-3 y 9-16 arriba mencionados produce un heterociclo que contiene una cadena lateral aminoalquilo apropiada para reaccionar con ácidos carboxílicos apropiadamente substituidos, por ejemplo, ácido N-Boc tranexamico o ácido 4-cianobenzoico, bajo condiciones de acomplamiento de enlace amida estándar (Esquema de reacción 17A). Las combinaciones de reactivo comúnmente empleadas para esta transformación pueden usarse e incluyen, pero no se limitan a: reactivo BOP y piridina; EDCI, HOAt, N-metil morfolina; o EDCI, HOBt, N-metil morfolina. Los solventes apropiados para esta transformación incluyen, pero no se limitan a, piridina, THF y dimetilformamida. Las combinaciones de solventes pueden también usarse tales como diclorometano y DMF en relaciones apropiadas para alcanzar la solubilidad de los reactivos apropiados. Alternativamente, las aminas a partir de los Esquemas de reacción 1-3 y 9-16 pueden hacerse reaccionar con agentes alquilantes apropiados substituidos o haluros de sulfonilo, usando métodos conocidos por alguien experto en el arte. Se reconocerá que las etapas de desprotección adicionales y manipulaciones de grupos funcionales adicionales de los compuestos obtenidos por medio del Esquema de reacción 17 usando métodos conocidos en el arte, proporcionarán entonces compuestos adicionales de esta invención.

Alternativamente, cuando el heterociclo contiene un

ácido carboxílico alifático que contiene una cadena lateral, la formación de enlace amida puede efectuarse por la reacción de una amina o anilina apropiadamente substituida con las combinaciones de reactivo descritas en la presente (Esquema de reacción 17B).

Esquemas de reacción 17A y 17B

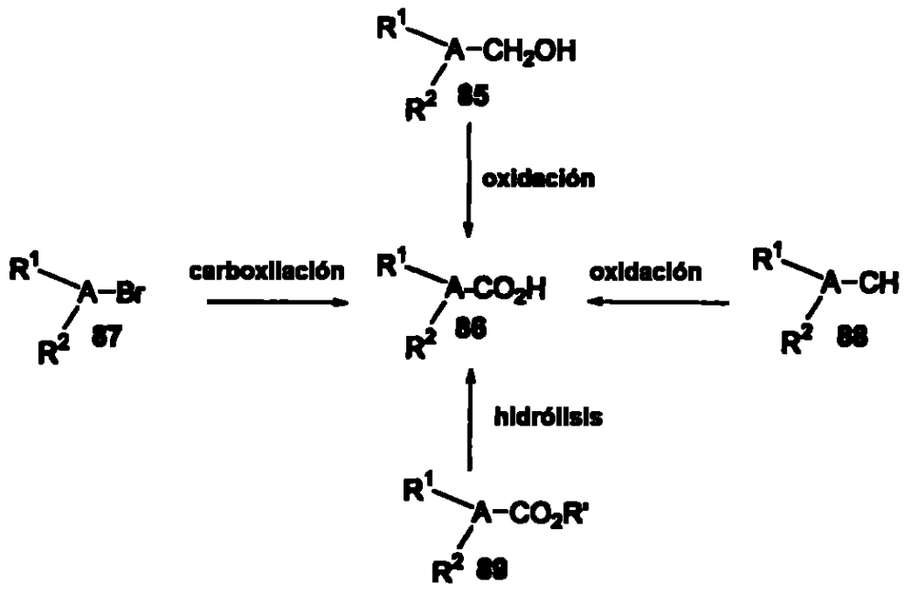


El ácido carboxílico apropiadamente substituido ($A-CO_2H$) se usa en el acoplamiento de amida mostrado en el Esquema de reacción 17A. Muchos de estos ácidos carboxílicos están comercialmente disponibles. En el caso en donde los ácidos carboxílicos no están comercialmente disponibles, pueden prepararse a partir del correspondiente bromuro 87, alcohol 85, aldehído 88, o éster 89 como se muestra en el Esquema de reacción 18 usando métodos conocidos en el arte. Los grupos R^1 y R^2 pueden manipularse además usando métodos conocidos en el arte para proporcionar compuestos adicionales de esta invención. Por ejemplo, el grupo ciano puede usarse como R^1,

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que puede reducirse para dar CH_2NH_2 con un agente reductor apropiado o convertirse a la amidina por la reacción con hidroxilamina, y seguido por hidrogenación catalizada por paladio usando los métodos previamente descritos.

Esquema de reacción 18

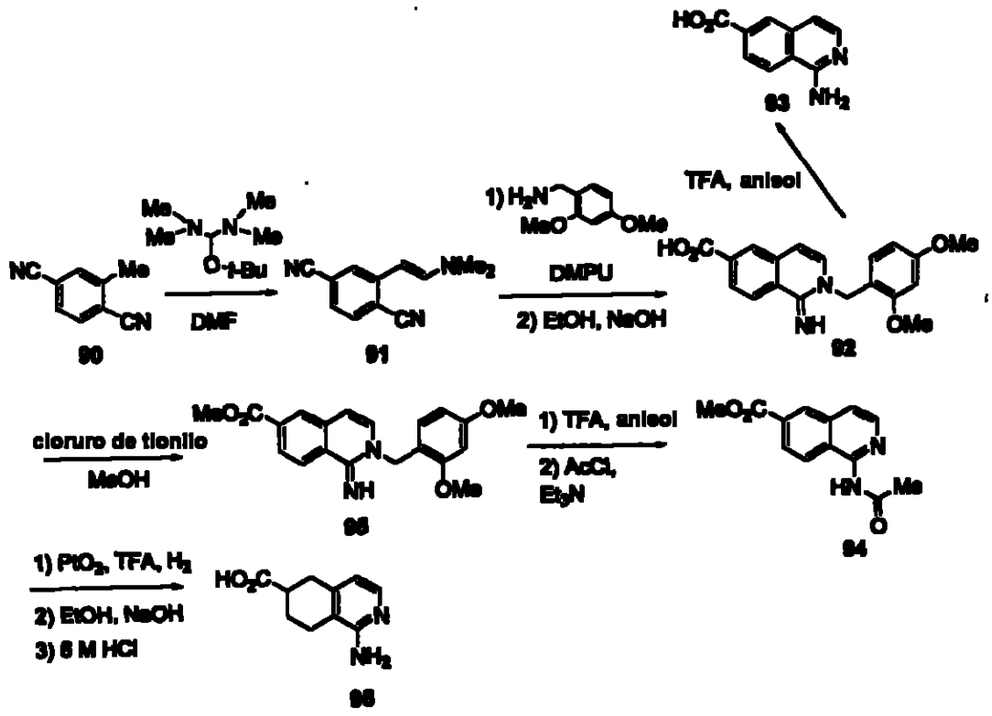


Cuando A es una porción isoquinolina, se sigue un procedimiento modificado a partir de US2004/0077865. El calentamiento del derivado de 2-metil benzonitrilo 90 con 1-(t-butoxi)-N,N,N',N'-tetrametilmetanodiamina en un solvente apropiado tal como DMF da la enamina 91. La condensación de la enamina 91 y 2,4-dimetoxibencilamina en DMPU a temperaturas elevadas da el esqueleto 1-imino-1,2-dihidroisoquinolina y la posterior hidrólisis proporciona el 92. La desbencilación del 92 con anisol en TFA a temperaturas elevadas proporciona la 1-

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amino-isoquinolina 93. Cuando A es una porción 5,6,7,8-tetrahidroisoquinolina, un procedimiento modificado de McEachern et al. se sigue (J. Org. Chem. 2002, 67, 7890). El ácido 92 se convierte al éster 94. La desbencilación del 94 con anisol en TFA a temperaturas elevadas y la acetilación con cloruro de acetilo y trietilamina proporciona el 95. La hidrogenación sobre óxido de platino en la presencia de TFA proporciona la 1-amino-5,6,7,8-tetrahidroisoquinolina. La saponificación del éster con NaOH e hidrólisis de la amida bajo condiciones ácidas da el 96.

Esquema de reacción 19

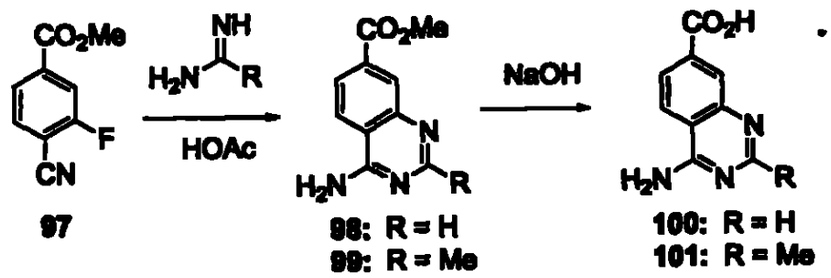


Cuando A es una porción 4-aminoquinazolina, el

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calentamiento de un orto-fluoro benzonitrilo 97 apropiadamente substituido con acetato de formamidina o acetato de acetamidina en DMA, de conformidad con un procedimiento modificado de Lam (Lam, P.Y.S. et al. J. Med. Chem. 2003, 46, 4405.), produce la 4-aminoquinazolina 98 y 99. La saponificación del éster bajo condiciones básicas proporciona el 100 y 101.

Esquema de reacción 20



97 98: R = H 99: R = Me 100: R = H 101: R = Me

Otras características de la invención serán aparentes en el curso de las siguientes descripciones de modalidades ejemplares que se dan para la ilustración de la invención y no se pretende que sean limitantes de la misma.

EJEMPLOS

La relación de solución expresa una relación de volumen, salvo que se establezca de otra manera. Los cambios químicos de RMN (δ) se reportan en partes por millón. La cromatografía instantánea se lleva a cabo en gel de sílice de conformidad con el método de Still (Still, W. C. et al. J. Org. Chem.

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1978, 43, 2923).

Como se usa a través de la especificación, se aplican las siguientes abreviaturas para los reactivos químicos:

HOAc o AcOH = ácido acético

Bn = bencilo

Bu = butilo

t-Bu = butilo terciario

Boc = terc-butil oxicarbonilo

Reactivo BOP = hexafluorofosfato de benzotriazol-1-iloxi-tris(dimetilamino)fosfonio

Salmuera = cloruro de sodio acuoso saturado

CSA = ácido canfor sulfónico

DMF = dimetilformamida

DMSO = dimetil sulfóxido

EDCI = clorohidrato de 1-(3-(dimetilamina)propil)-3-etilcarbodiimida

Et = etilo

EtOH = etanol

EtOAc = acetato de etilo

Me = metilo

MeOH = metanol

NaOAc = acetato de sodio

OAc = acetato

Ph = fenilo

Pr = propilo

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i-Pr = isopropilo

i-PrOH = isopropanol

TFA = ácido trifluoroacético

THF = tetrahidrofurano

°C = grados centígrados

atm = atmósfera

conc. = concentrado

eq = equivalente(s)

h o hr = hora(s)

g = gramo(s)

mg = miligramo(s)

L = litro(s)

mL = mililitro(s)

µL = microlitro(s)

mmol = milimolar

M = molar

meq = miliequivalente(s)

min. = minuto(s)

PM = peso molecular

pf = punto de fusión

ta o TA = temperatura ambiente

sat o sat'd = saturado

ESI = espectroscopía de masa de ionización de electrorocío

CLAR = cromatografía líquida de alta resolución

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EM = espectrometría de masa

CL/EM = cromatografía líquida espectrometría de masa

EMAR = espectrometría de masa de alta resolución

RMN = espectroscopía de resonancia magnética nuclear

CCD = cromatografía de capa delgada

"α", "β", "R", "S", "E", y "Z" son designaciones estereoisoméricas familiares para alguien experto en la técnica. Un estereoisómero de un compuesto de la Fórmula I puede exhibir una actividad superior en comparación con los otros. De esta manera, cada estereoisómero de un compuesto de la Fórmula I se considera que es parte de la presente invención. Cuando se requiere, la separación del material racémico puede realizarse por CLAR usando una columna quiral o por resolución usando un agente de resolución tal como se describe en Wilen, S. H. Tables of Resolving Agents y Optical Resolutions 1972, 308 o usando ácidos y bases enantioméricamente puras. Un compuesto quiral de la Fórmula I también puede sintetizarse directamente usando un catalizador quiral o un ligando quiral, por ejemplo, Jacobsen, E. Acc. Chem. Res. 2000, 33, 421-431 o usando otras reacciones y reactivos enantio- o diaestereo-selectivos conocidos por aquellos expertos en el arte de la síntesis asimétrica.

Los siguientes ejemplos se han preparado, aislado y

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caracterizado usando los métodos descritos en la presente. Los siguientes Ejemplos demuestran un alcance parcial de la invención y no son un medio para limitar el alcance de la invención.

Ejemplo 1

(S)-4-carbamimidoil-N-(2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)benzamida, sal del ácido bistrifluoroacético

Parte A: 2-fenil-1-(4-fenil-1H-imidazol-2-il)etilcarbamato de (S)-terc-butilo: A una solución de L-N-(Boc)-fenilalanina (750 mg, 3.77 mmol) en EtOH/H_2O (1:1; 7.4 mL) se le agregó Cs_2CO_3 (650 mg, 1.89 mmol). La reacción se agitó a temperatura ambiente durante 1 hora. El solvente se removió bajo vacío y la sal resultante se suspendió en DMF (4.7 mL). La 2-bromoacetofenona (1.0 g, 3.77 mmol) se agregó en una porción sencilla y la reacción se agitó a temperatura ambiente durante 1.5 hora. La reacción se filtró para remover el CsBr. Los sólidos se lavaron con DMF. Los lavados combinados y el filtrado se concentraron in vacuo para proporcionar un sólido amarillo (650 mg). El intermediario crudo se colocó en un matraz equipado con una trampa Dean-Stark y se disolvió en xilenos (10 mL). El NH_4OAc (2.64 g, 30 mmol) se agregó al matraz y la reacción se calentó hasta reflujo durante 3 horas. La reacción se enfrió hasta temperatura ambiente y el solvente se removió in vacuo. El

residuo se volvió a disolver en EtOAc y se lavó con $NaHCO_3$ acuoso saturado y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse para proporcionar 780 mg del producto deseado (57% de rendimiento). EM 364.2 $(M+H)^+$.

Alternativamente, el intermediario ceto éster y 10 equivalentes de NH_4OAc se disolvieron en etanol y se calentaron hasta 160°C en un tubo sellado durante 30 minutos usando irradiación de microondas. La reacción se enfrió hasta temperatura ambiente, el etanol se evaporó in vacuo y el residuo se volvió a disolver en EtOAc. La capa orgánica se lavó con salmuera ½ saturada (2 veces), se secó sobre $MgSO_4$ y se evaporó hasta secarse. El producto crudo de esta manera formado fue suficientemente puro para llevarse a la siguiente etapa.

Parte B: sal del ácido bis-trifluoroacético de (S)-2-fenil-1-(4-fenil-1H-imidazol-2-il)etanamina: El producto del Ejemplo 1 Parte A (100 mg, 0.28 mmol) se disolvió en CH_2Cl_2 (2.8 mL) y se trató con TFA puro (0.2 mL, 10% v/v). La reacción se agitó a temperatura ambiente durante 16 horas. El solvente y TFA se removieron in vacuo. El residuo se volvió a disolver en metanol. El solvente se removió in vacuo, el residuo se volvió a disolver en MeOH y el solvente se evaporó in vacuo para proporcionar 124 mg (92% de rendimiento) de la amina cruda como la sal bis-TFA. EM 262.2 $(M-H)^-$.

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Parte C: (S)-4-carbamimidoil-N-(2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)benzamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 1 Parte B (124 mg, 0.25 mmol) y clorohidrato del ácido 4-amidinobenzoico (94 mg, 0.47 mmol) se disolvieron en piridina anhidra (2 mL). El reactivo BOP (249 mg, 0.56 mmol) se agregó y la reacción se agitó a temperatura ambiente durante 16 horas. El solvente se removió in vacuo y el residuo se volvió a disolver en MeOH/H_2O (9:1) que contiene TFA al 0.1%. La solución se filtró y el compuesto del título se aisló por CLAR preparativa para proporcionar 9.2 mg del producto deseado (3% de rendimiento). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 3.37 (dd, J = 8.5 y 13 Hz, 1H), 3.46 (dd, J = 8.5 y 13 Hz, 1H), 5,48 (app t, J = 8.2 Hz, 1H), 7.14-7.21 (m, 5H), 7.34-7.41 (m, 3H), 7.56 (m, 2H), 7.68 (s, 1H), 7.80 (d, J = 8.2 Hz), 7.96 (d, J = 8.2 Hz, 2H): EMAR $(M + H)^+$ para $C_{25}H_{23}N_5O$, m/z calculado: 410.1981, obs: 410.1974.

Ejemplo 2

(S)-4-(aminometil)-N-(2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético

Parte A: (4-((2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)carbamoil)ciclohexil)metilcarbamato de (S)-terc-butilo: El producto del Ejemplo 1 Parte B (75 mg, 0.15 mmol)

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y ácido N-(Boc)-tranexámico (75 mg, 0.29 mmol) se disolvieron en piridina (1.7 mL). El reactivo BOP (152 mg, 0.344 mmol) se agregó y la reacción se agitó a temperatura ambiente durante 12 horas. La reacción se diluyó con agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se evaporaron in vacuo. El producto crudo se llevó a la siguiente etapa sin purificación adicional. EM 503.2 $(M+H)^+$.

Alternativamente, el producto del Ejemplo 1 Parte B se acopló con 1.0 equivalente de ácido N-Boc-tranexámico, 1.2 equivalentes de HOAt, 5.0 equivalentes de N-metilmorfolina, y 1.2 equivalente de EDCI. La amina, ácido N-Boc-tranexámico y HOAt se disolvieron en DMF. La N-metilmorfolina se agregó seguido por EDCI. La reacción se agitó a temperatura ambiente durante 2 y 16 horas. La reacción se diluyó con EtOAc, se lavó con salmuera ½ saturada (4-6 veces), se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse para dar el producto crudo.

Parte B. (S)-4-(aminometil)-N-(2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 2 Parte A (100 mg) se disolvió en TFA al 30% en CH_2Cl_2 (2.0 mL). La reacción se agitó a temperatura ambiente durante 3 horas. La reacción se diluyó con tolueno y se secó in vacuo. El residuo se

volvió a disolver en tolueno y la solución se evaporó hasta secarse. El producto crudo se volvió a disolver en MeOH/H_2O (9:1) que contiene TFA al 0.1% y el compuesto del título se aisló por CLAR preparativa (46 mg como la sal bis-TFA, 49% de rendimiento). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.02-1.11 (m, 2H), 1.32-1.45 (m, 2H), 1.54-1.61 (m, 1H), 1.80 (br d, J = 12.1 Hz, 1H), 1.86 (br d, J = 11.5 Hz, 3H), 2.28 (dt, J = 12.1, 3.30 Hz, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.28-3.33 (dd, 1H, oscurecido por pico de CH_3OH), 3.38 (dd, J = 13.5, 8.0 Hz), 5.31 (t, J = 8.25 Hz, 1H), 7.18 (d, J = 7.15 Hz, 2 H), 7.22-7.30 (m, 3H), 7.43-7.50 (m, 3H), 7.62 (app d, J = 6.6 Hz, 2H), 7.75 (s, 1H): EM 403.2 $(M + H)^+$.

Ejemplo 25

2-(4-(2-(1-(4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)fenil)acetato de (S)-etilo, sal del ácido bistrifluoroacético

Parte A: 4-acetil-fenilacetato de etilo: El bromoacetato de etilo (1.70 g, 10.2 mmol), tris-(1-naftilen)fosfina (379 mg, 0.93 mmol) y fosfato de potasio tribásico (10.8 g, 51 mmol) se colocaron en un matraz. El matraz se evacuó y se volvió a rellenar con argón. Una solución de ácido 4-acetilfenilborónico (2.0 g, 12.2 mmol) en THF anhidro (40 mL) se agregó al matraz. La reacción se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con EtOAc,

se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse. El residuo se adsorbió previamente en SiO_2 y el producto se aisló por medio de cromatografía en SiO_2 para proporcionar 616 mg (29%) del 4-acetil-fenilacetato de etilo. EM 207.1 $(M+H)^+$.

Parte B: 2-(4-(2-bromoacetil)fenil)acetato de etilo: El 4-acetil-fenilacetato de etilo del Ejemplo 25 Parte A (489 mg, 2.4 mmol) se disolvió en CH_2Cl_2. El bromo (379 mg, 2.4 mmol) se agregó gota a gota. La reacción se agitó a temperatura ambiente durante 16 horas. La reacción se decoloró a partir de rojizo hasta amarillo ligero. El solvente se evaporó in vacuo para proporcionar 680 mg (99%) de 2-(4-(2-bromoacetil)fenil)acetato de etilo como un aceite amarillo ligero. El producto se usó en la siguiente etapa sin purifiación adicional. EM 287.0 y 289.0 de intensidades iguales $(M+H)^+$.

Parte C: 2-(4-(2-(1-(terc-butoxicarbonil)-2-feniletil)-1H-imidazol-4-il)fenil)acetato de (S)-etilo: La N-(Boc)-fenilalanina (633 mg, 2.38 mmol) se disolvió en DMF (2.0 mL). El Cs_2CO_3 (775 mg, 1.19 mmol) se agregó al matraz en una porción sencilla, y la reacción se agitó durante 1 hora. Una solución de 2-(4-(2-bromoacetil)fenil)acetato de etilo del Ejemplo 25 Parte B (680 mg, 2.38 mmol) en DMF (2.0 mL) se

agregó a un recipiente de reacción, y la reacción se agitó, a temperatura ambiente durante 16 horas. Los sólidos se filtraron completamente y se enjuagaron con DMF. Las capas orgánicas se combinaron y se evaporaron hasta secarse. El residuo se volvió a disolver en EtOAc y se lavó con una solución de 1:1 agua y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar 1.03 g de un sólido color marrón ligero. El sólido se volvió a disolver en xilenos (14 mL). El NH_4OAc (3.42 g, 44 mmol) se agregó, y el matraz se equipó con una trampa Dean-Stark. La reacción se calentó hasta reflujo durante 5 horas con remoción de agua. La reacción se enfrió hasta temperatura ambiente, y el solvente se removió in vacuo. El residuo se volvió a disolver en EtOAc, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar 951 mg (96%) de un sólido color marrón ligero EM 450.1 $(M+H)^+$.

Parte D: 2-(4-(2-(1-amino-2-feniletil)-1H-imidazol-4-il)fenil)acetato de (S)-etilo: El producto del Ejemplo 25 Parte C (951 mg, 2.12 mmol) se trató de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B para proporcionar 1.14 g (100%) de un vidrio café oscuro, el cual se usó sin purificación en la siguiente etapa. EM 333.1 $(M-NH_2)^+$.

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Parte E: 2-(4-(2-(1-(4-((terc-butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)fenil)acetato de (S)-etilo: El producto del Ejemplo 25 Parte D (729 mg, 1.26 mmol), ácido N-(Boc)-tranexámico (325 mg, 1.26 mmol) y HOAt (206 mg, 1.51 mmol) se disolvieron en DMF (6.3 mL). La N-metilmorfolina (637 mg, 6.3 mmol) se agregó seguido por EDCI (289 mmol, 1.51 mmol). La reacción se agitó a temperatura ambiente durante 16 horas, se diluyó con EtOAc, se lavó con una mezcla 1:1 de agua y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar 732 mg (99%) del producto, el cual se usó en la siguiente etapa sin purifiación adicional. EM 589.1 $(M+H)^+$.

Parte F: 2-(4-(2-(1-(4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)fenil)acetato de (S)-etilo, sal del ácido bistrifluoroacético: El producto del Ejemplo 25 Parte E (99 mg, 0.17 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B. El producto se aisló por CLAR preparativa para proporcionar 61 mg (50%) del compuesto del título como la sal bis-TFA. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.02-1.11 (m, 2H), 1.24 (t, J = 7.15 Hz, 3H), 1.32-1.45 (m, 2H), 1.53-1.61 (m, 1H), 1.80 (br d, J = 12.6 Hz, 1H), 1.86 (br d, J = 11.0 Hz, 3H), 2.28 (tt, J = 12.4, 3.0 Hz, 1H), 2.775 (d, J = 7.15 Hz, 2H), 3.28-3.32 (dd,

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oscurecido por pico MeOH), 3.38 (dd, J = 13.5, 8.0 Hz, 1 H), 3.70 (s, 2H), 4.145 (q, J = 7.15 Hz, 2H), 5.31 (t, J = 8.5 Hz, 1H), 7.175 (d, J = 7.15 Hz, 2H), 7.22-7.30 (m, 3H), 7.41 (d, J = 8.25, 2H), 7.59 (d, J = 8.25 Hz, 2H), 7.74 (s, 1H). EMAR $(M + H)^+$ para $C_{29}H_{36}N_4O_3$, m/z calculado: 489.2866, obs: 489.2861.

Ejemplo 26

Ácido (S)-2-(4-(2-(1-(4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)fenil)acético, sal del ácido bistrifluoroacético

La sal del ácido bis trifluoroacético del 2-(4-(2-(1-(4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)fenil)acetato de (S)-etilo del Ejemplo 25 (30 mg, 0.042 mmol) se disolvió en MeOH (2 mL) y se trató con NaOH 1 N (0.2 mL). La reacción se agitó a temperatura ambiente durante 16 horas. El solvente se removió in vacuo y el residuo se volvió a disolver en $MeOH/H_2O$ (9:1) que contiene TFA al 0.1% y luego se purificó por CLAR preparativa para proporcionar 22 mg del compuesto del título como su sal bis-TFA (76% de rendimiento). ^1H-RMN (500 MHz, d_4-MeOH) δ 1.02-1.11 (m, 1H), 1.31-1.45 (m, 2H), 1.53-1.61 (m, 1H), 1.79 (br d, J = 12.1 Hz, 1H), 1.865 (br d, J = 12.1 Hz, 3H), 2.28 (tt, J = 3.2 y 12.1 Hz, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.28-3.32 (dd, oscurecido por pico MeOH), 3.375 (dd, J = 8.0 y 13.4 Hz, 1

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H), 3.67 (s, 2H), 5.31 (t, J = 8.25 Hz, 1H), 7.175 (d, J = 6.6 Hz, 2H), 7.22-7.30 (m, 3H), 7.42 (d, J = 8.25 Hz, 2H), 7.59 (d, J = 8.25 Hz, 2H), 7.74 (s, 1H). EMAR $(M + H)^+$ para $C_{27}H_{32}N_4O_3$, m/z calculado: 461.2553, obs: 461.2572.

Ejemplo 27

(S)-4-(aminometil)-N-{1-[(4-carbamoilmetil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-ciclohexancarboxamida, sal del ácido bistrifluoroacético

Parte A: ácido (S)-2-(4-(2-(1-(4-((terc-Butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)fenil)acético: El producto del Ejemplo 25 Parte E (200 mg, 0.34 mmol) se disolvió en MeOH (3 mL) y se trató con NaOH 1 N (0.34 mL). La reacción se agitó a temperatura ambiente durante 16 horas. El solvente se removió in vacuo. El residuo se volvió a disolver en $MeOH/H_2O$ (9:1) que contiene TFA al 0.1%. El producto se aisló por CLAR preparativa (90 mg, 47%). EM 561.1 $(M+H)^+$.

Parte B: (4-((1-(4-(4-(2-amino-2-oxoetil)fenil)-1H-imidazol-2-il)-2-feniletil)carbamoil)ciclohexil)metilcarbamato de (S)-terc-butilo: El producto del Ejemplo 27 Parte A (33 mg, 0.060 mmol) y HOAt (9.7 mg, 0.071 mmol) se disolvieron en DMF (1 mL). La N-metilmorfolina (18.2 mg, 0.18 mmol) y EDCI (13.6

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mg, 0.071 mmol) se agregaron secuencialmente. La reacción se agitó durante 30 minutos a temperatura ambiente. El amoniaco acuoso concentrado (5 gotas de una pipeta Pasteur) se agregó y la reacción se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con EtOAc y se lavó con una mezcla 1:1 de agua y salmuera (5x), HCl acuoso 1 N y salmuera, se secó sobre $MgSO_4$, se filtró y se secó in vacuo. El residuo se volvió a disolver en $MeOH/H_2O$ (9:1) que contiene TFA al 0.1%, y el producto se aisló por CLAR preparativa para proporcionar 9 mg (22%). EM 560.1 $(M+H)^+$.

Parte C: (S)-N-(1-(4-(4-(2-amino-2-oxoetil)fenil)-1H-imidazol-2-il)-2-feniletil)-4-(aminometil)-ciclohexanecarboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 27 Parte B (9 mg, 0.016 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B para proporcionar el compuesto del título (11 mg,99%). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.02-1.11 (m,2H), 1.28-1.44 (m, 2H), 1.57 (m, 1H), 1.79 (br d, J = 12.6 Hz, 1H), 1.85 (br d, J = 11 Hz, 3H), 2.28 (tt, J = 3.0, 12.1 Hz, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.28-3.32 (dd, oscurecido por MeOH), 3.375 (dd, J=8.0, 13.0Hz, 1H), 3.57 (s, 2H), 5.31 (t, J=8.2Hz, 1H), 7.175 (d, J = 7.2 Hz, 2H), 7.22-7.30 (m, 3H), 7.43 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.74 (s, 1H); EMAR $(M + H)^+$ para $C_{27}H_{33}N_5O_2$, m/z calculado: 460.2713,

obs: 460.2714.

Ejemplo 28

4-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)benzamida, sal del ácido bistrifluoroacético

Parte A: (trans-4-(((S)-1-(4-(4-carbamoilfenil)-1H-imidazol-2-il)-2-feniletil)carbamoil)ciclohexil)metilcarbamato de terc-butilo: El (trans-4-(((S)-1-(4-(4-cianofenil)-1H-imidazol-2-il)-2-feniletil)carbamoil)ciclohexil)metilcarbamato de terc-butilo formado a partir de la 2-bromo-4'-cianoacetofenona usando los procedimientos del Ejemplo 1 Parte A-B y Ejemplo 2 Parte A (117 mg, 0.22 mmol) se disolvió en DMSO (2 mL) y se trató con K_2CO_3 (90.0 mg, 0.65 mmol) bajo argón. El H_2O_2 al 30% en agua (0.8 mL, 2.4 mmol) y óxido de magnesio (44 mg, 1.11 mmol) se agregaron secuencialmente a la reacción. La reacción se agitó a temperatura ambiente durante 4 horas. La reacción se diluyó con EtOAc, se lavó con HCl 1 N y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse. El producto (109 mg, 90% de rendimiento) se aisló como un sólido amarillo. EM 546.3 $(M+H)^+$.

Parte B: 4-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido-2-feniletil)-1H-imidazol-4-

il)benzamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 28 Parte A (109 mg, 0.20 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 2 Parte B. El producto se aisló por CLAR preparativa para proporcionar 17.3 mg del compuesto del título (20%). ^{1}H RMN (500 MHz, d_4-MeOH) δ 0.36 (m, 2 H), 0.68 (m, 2 H), 0.87 (m, 1 H), 1.14 (m, 3 H), 2.07 (d, J = 7.15 Hz, 2 H), 2.63 (m, 2H), 4.61 (t, J = 8.25 Hz, 1 H), 6.47 (d, J = 7.15 Hz, 2 H) ,6.53 (t, J = 7.42 Hz, 1 H),6.58 (t, J = 7.15 Hz, 2 H), 7.04 (d, J = 8.25 Hz, 2 H), 7.14 (s, 1 H), 7.28 (d, J = 8.25 Hz, 2 H); EMAR $(M + H)^+$ para $C_{26}H_{31}N_5O_2$, m/z calculado: 446.2556, obs: 446.2570.

Ejemplo 29

3-(2-((S)-1-(4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)benzamida, sal del ácido bistrifluoroacético

El compuesto del título se sintetizó por la aplicación apropiada del procedimiento descrito por el Ejemplo 28. ^{1}H RMN (500 MHz, d_4-MeOH) δ 1.06 (m, 2H), 1.39 (m, 2 H), 1.57 (m, 1 H), 1.80 (d, J = 12.10 Hz, 1 H), 1.86 (d, J = 11.55 Hz, 3 H), 2.28 (tt, J= 12.10, 3.30 Hz, 2 H), 2.77 (d, J = 7.15 Hz, 2 H), 3.34 (d, J = 8.25 Hz, 1 H), 3.39 (dd, J = 13.40, 8.25 Hz, 1 H), 3.98 (s, 1 H), 5.34 (t, J = 8.25Hz, 1 H), 7.19 (d, J = 6.60 Hz, 2 H), 7.24 (t, J = 7.15 Hz, 1 H), 7.29 (t, J

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= 7.15 Hz, 2 H), 7.60 (t, J = 7.70 Hz, 1 H), 7.82 (m, J = 5.50 Hz, 2 H), 7.93 (d, J = 8.25 Hz, 1 H) 8.18 (s, 1 H); EM 446.2 $(M+H)^+$.

Ejemplo 30

4-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)-N-metilbenzamida, sal del ácido bistrifluoroacético

Parte A: ácido 4-(2-((S)-1-(trans)-4-((terc-butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)benzoico: El 4-(2-((S)-1-(trans-4-((terc-butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)benzoato de metilo formado a partir de 2-bromo-4'-carboximetilacetofenona usando los procedimientos del Ejemplo 1 Parte A-B y Ejemplo 2 Parte A (162 mg, 0.28 mmol) se disolvió en MeOH (5 ml) y EtOAc (1 mL). El NaOH 1 N (2 mL) y óxido de magnesio (112 mg, 2.8 mmol) se agregaron secuencialmente y la mezcla se agitó durante 5 horas a temperatura ambiente. El solvente se evaporó hasta secarse in vacuo. El residuo se diluyó con agua y se trató con HCl 1 N. La solución resultante se diluyó con EtOAc, se lavó con salmuera y se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar 75 mg (60 % de rendimiento) de un vidrio claro. EM 548.0 $(M+H)^+$.

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Parte B: (trans)-4-(((S)-1-(4-(4-(metilcarbamoil)fenil)-1H-imidazol-2-il)-2-feniletil)carbamoil)ciclohexil)metilcarbamato de terc-butilo: El producto del Ejemplo 30 Parte A (45 mg, 0.08 mmol) y metilamina (0.2 mL, 0.09 mmol) se trataron bajo las condiciones descritas en el Ejemplo 2 Parte B con la substitución de HOBt por HOAt. El aceite amarillo resultante (44.0. mg, 93% de rendimiento) se llevó a la siguiente etapa sin purificación adicional. EM 560.1 $(M+H)^+$.

Parte C: 4-(2-((S)-1-(trans)-4-(aminometil)ciclohexancarboxamido-2-feniletil)-1H-imidazol-4-il)-N-metilbenzamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 30 Parte B (44.0 mg, 0.079 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 2 Parte B. El residuo resultante se volvió a disolver en $MeOH/H_2O$ (9:1) que contiene TFA al 0.1% y se aisló por CLAR preparativa para proporcionar 1.0 mg del compuesto del título (3%). ^1H RMN (500 MHz, d_4-MeOH) δ 1.05 (m, 1 H), 1.39 (ddd, J = 30.24, 12.92, 3.02 Hz, 1 H), 1.55 (m, J = 12.10 Hz, 1 H), 1.79 (m, 1 H), 1.86 (d, J = 11.00 Hz, 1 H), 2.26 (m, 1 H), 2.77 (d, J = 7.15 Hz, 1 H), 2.92 (s, 1 H), 3.15 (m, 1 H), 3.3 (m, 2H), 5.29 (t, J = 8.25 Hz, 1 H), 7.16 (d, J = 7.15 Hz, 1 H), 7.23 (t, J = 7.15 Hz, 1 H), 7.28 (t, J = 7.15 Hz, 1 H), 7.72 (d, J = 8.25 Hz, 1 H),7.86 (s, 1

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H), 7.92 (d, J = 8.80 Hz, 1 H); EMAR $(M + H)^+$ para $C_{27}H_{33}N_5O_2$, m/z calculado: 460.2713, obs: 460.2735.

Ejemplo 31 (S)-4-(2-(1-trans-(4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)-N,N-dimetilbenzamida, sal del ácido bistrifluoroacético

El compuesto del título se sintetizó por la aplicación apropiada del procedimiento descrito por la síntesis del Ejemplo 30. ^1H RMN (500 MHz, d_4-MeOH) δ 1.06 (m, 2 H), 1.39 (m, 2 H), 1.57 (m, 1 H), 1.81 (d, J = 14.85 Hz, 1 H), 1.86 (d, J = 10.45 Hz, 3 H), 2.28 (tt, J = 12.30, 3.30 Hz, 1 H), 2.77 (d, J = 7.15 Hz, 2 H), 3.01 (s, 3 H), 3.12 (s, 3 H), 3.39 (dd, J = 13.30, 8.24 Hz, 1 H), 5.31 (t, J = 8.25 Hz, 1 H), 7.18 (d, J = 7.15 Hz, 2 H), 7.24 (t, J = 7.15 Hz, 1 H), 7.29 (t, J = 7.42 Hz, 2 H), 7.55 (d, J = 8.25 Hz, 2 H), 7.72 (d, J = 8.25 Hz, 2 H), 7.85 (s, 1 H); EMAR $(M + H)^+$ para $C_{28}H_{35}N_5O_2$, m/z calculado: 474.2870, obs: 474.2875.

Ejemplo 32

trans-N-((S)-1-(4-(1H-benzo[d]imidazol-2-il)-1H-imidazol-2-il)-2-feniletil)-4-(aminometil)ciclohexancarboxamida, sal del ácido tristrifluoroacético

Parte A: 2-fenil-1-(4-(trifluorometil)-1H-imidazol-2-il)etilcarbamato de (S)-terc-butilo: A una solución de acetato de sodio (0.88 g, 6.44 mmol) en 3 mL de agua se le

agregó 1,1-dibromotrifluoroacetona (0.87 g, 3.22 mmol). La mezcla se calentó a 90°C bajo N_2 durante 30 minutos. Se enfrió hasta 0°C y la solución de (S)-(-)-2-(t-butoxicarbonilamino)-3-fenilpropanal (1.73 g, 2.93 mmol) en 15 mL de metanol se agregó, seguido por hidróxido de amonio concentrado (4 mL de solución concentrada). La mezcla resultante se agitó a temperatura ambiente bajo N_2 durante 12 horas. El solvente se removió y el agua se agregó. El precipitado se filtró y luego se volvió a disolver en EtOAc. La solución de EtOAc se lavó con salmuera, se secó sobre Na_2SO_4, y se filtró. El filtrado se concentró para dar 0.80 g del producto deseado como un sólido blanco opaco (76.9% de rendimiento). EM, 356.30 $(M+H)^+$.

Parte B: 2-fenil-1-(4-(trimetoximetil)-1H-imidazol-2-il)etilcarbamato de (S)-terc-butilo: El producto del Ejemplo 32 Parte A (0.1 g, 0.4 mmol) se disolvió en MeOH (2 mL) y se trató con NaOMe (25% en peso en MeOH, 1.7 mL, 7.4 mmol). La mezcla de reacción se calentó usando irradiación de microondas en un tubo sellado durante 5 minutos a 100°C. Durante el enfriamiento hasta temperatura ambiente, el solvente se removió bajo vacío, y el residuo se disolvió en EtOAc (15 mL). La solución se lavó con H_2O, salmuera, se secó sobre Na_2SO_4, se filtró, y se evaporó hasta secarse para proporcionar una goma café (0.15 g). EM 392.1 $(M+H)^+$.

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Parte C: (trans-4-(((S)-1-(4-(1H-benzo[d]imidazol-2-il)-1H-imidazol-2-il)-2-feniletil)carbamoil)ciclohexil)metilcarbamato de terc-butilo: El intermediario crudo del Ejemplo 32 Parte B se disolvió en THF (2 mL). La 1,2-fenilendiamina (41 mg, 0.38 mmol) y monohidrato del ácido p-toluensulfónico (7.3 mg, 0.038 mmol) se agregaron a la reacción. La reacción se agitó a temperatura ambiente durante 6 horas, y el solvente se removió in vacuo. El residuo se disolvió en EtOAc y se lavó con $NaHCO_3$ acuoso saturado y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse. El residuo se purificó por cromatografía instantánea (gel de sílice, 0-100% EtOAc en gradiente de hexano) para proporcionar 59 mg (37%), como un sólido amarillo. EMAR m/z Calculado para $C_{23}H_{26}N_5O_2$ $[M + H]^+$: 404.2087. Encontrado 404.2079.

Parte D: trans-N-((S)-1-(4-(1H-benzo[d]imidazol-2-il)-1H-imidazol-2-il)-2-feniletil)-4-(aminometil)ciclohexancarboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 32 Parte C (59 mg, 0.15 mmol) se disolvió en CH_2Cl_2 (0.7 mL) y se trató con TFA puro (0.3 mL, 30% v/v). La reacción se agitó a temperatura ambiente durante 1 hora. El solvente y TFA se removieron in vacuo. El residuo se volvió a disolver en DMF (1 mL). El Et_3N (0.073 mL, 0.53 mmol), ácido N-Boc-tranexámico (42 mg, 0.16 mmol), HOBt (0.03 g, 0.23 mmol), y

EDCI (43 mg, 0.23 mmol) se agregaron y la reacción se agitó a temperatura ambiente durante 4 horas. El EtOAc (15 mL) se agregó, seguido por H_2O (10 mL). La fase orgánica separada se lavó con agua, salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse. El residuo se disolvió en CH_2Cl_2 (0.7 mL) y se trató con TFA puro (0.3 mL, 30% v/v). Después de 40 minutos a temperatura ambiente, la reacción se concentró. La purificación por CLAR preparativa dio 66 mg (56 %) del compuesto del título. ^{1}H-RMN (400 MHz, CD_3OD) δ 0.99-1.09 (m, 2 H), 1.27-1.49 (m, 2 H), 1.54-1.60 (m, 1 H), 1.69-1.72 (m, 1 H), 1.82-1.85 (m, 3 H), 2.16-2.23 (m, 1 H), 2.76 (d, J = 7.0 Hz, 2 H), 3.20 (dd, J = 8.8, 13.6 Hz, 1 H), 3.46 (dd, J = 6.6, 13.6 Hz, 1 H), 5.35 (dd, J = 7.0, 8.8 Hz, 1 H), 7.16-7.26 (m, 5 H), 7.54-7.58 (m, 2 H), 7.72-7.76 (m, 2 H), 8.04 (s, 1 H); EMAR m/z Calculado para $C_{26}H_{31}N_6O$ $[M + H]^+$: 443.2559. Encontrado 443.2545.

Los Ejemplos 33-35 enlistados en la Tabla 2 se sintetizan similarmente por la aplicación apropiada del procedimiento descrito por el Ejemplo 32.

Ejemplo 36

2-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)tiazol-4-carboxilato de metilo, sal del ácido bistrifluoroacético

Parte A: 2-(2-((S)-1-(terc-butoxicarbonil)-2-feniletil)-

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1H-imidazol-4-il)-4,5-dihidrotiazol-4-carboxilato de metilo: 2-fenil-1-(4-(trifluorometil)-1H-imidazol-2-il)etilcarbamato de (S)-terc-butilo producido en el Ejemplo 32 Parte A (0.43 g, 1.21 mmol) se disolvió en MeOH (5 mL). El NaOMe (25% en peso en MeOH, 5.5 mL, 24.2 mmol) se agregó. La mezcla de reacción se calentó durante 42 horas a 60°C, luego se enfrió hasta temperatura ambiente. El solvente se removió bajo vacío, y el residuo se disolvió en EtOAc (50 mL). La solución se lavó con H_2O, salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse para proporcionar una goma café (0.54 g). Una porción del intermediario crudo (0.19 g) se disolvió en THF (5 mL). El clorohidrato de éster de L-cistein metilo (0.073 g, 0.43 mmol) y CSA (0.01 g, 0.043 mmol) se agregaron a la reacción. La reacción se agitó a temperatura ambiente durante 22 horas y el solvente se removió in vacuo. El residuo se purificó por cromatografía instantánea para proporcionar 0.022 g del producto deseado (12%) como un sólido amarillo. EM 431.08 $(M + 1)^+$.

Parte B. 2-(2-((S)-1-(terc-butoxicarbonil)-2-feniletil)-1H-imidazol-4-il)tiazol-4-carboxilato de metilo: El producto del Ejemplo 36 Parte A (0.022 g, 0.051 mmol) se disolvió en tolueno (1 mL) y se trató con MnO_2 (0.067 g, 0.77 mmol). La reacción se agitó a temperatura ambiente durante 5 horas. La mezcla de reacción se filtró, y la torta de filtro se lavó

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con EtOAc. Los filtrados combinados se concentraron hasta secarse. El residuo se purificó por cromatografía instantánea para proporcionar 0.017 g del triazol (78%) como un sólido blanco. EMAR m/z Calculado para $C_{21}H_{25}N_4O_5S$ $[M + H]^+$: 429.1597. Encontrado 429.1586.

Parte C: 2-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)tiazol-4-carboxilato de metilo, sal del ácido bistrifluoroacético: El producto del Ejemplo 36 Parte B se desprotegió con TFA, se acopló con ácido N-(Boc)-tranexámico, y luego se desprotegió siguiendo el mismo procedimiento descrito en el Ejemplo 32 Parte D para dar el compuesto del título, después de la purificación por CLAR preparativa (0.014 g, 50 %). ^{1}HRMN (400 MHz, CD_3OD) δ 0.96-1.10 (m, 2 H), 1.27-1.47 (m, 2 H), 1.51-1.61 (m, 1 H), 1.72-1.89 (m, 4 H), 2.18-2.28 (m, 1 H), 2.76 (d, J = 7.0 Hz, 2 H), 3.25-3.35 (m, 2 H), 3.94 (s, 3 H), 5.31 (t, J = 7.9 Hz, 1 H), 7.17-7.28 (m, 5 H), 7.98 (s, 1 H), 8.43 (s, 1 H); EMAR m/z Calculado para $C_{24}H_{30}Cl_2N_5O_3S$ $(M + H)^+$: 468.2069. Encontrado 468.2063.

Ejemplo 37

2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxilato de metilo, sal del ácido bistrifluoroacético

Parte A: 2-(1-amino-2-feniletil)-1H-imidazol-4-

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carboxilato de (S)-metilo: El producto formado en el Ejemplo 32 Parte B (492 mg, 1.43 mmol) se trató de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B para proporcionar 350 mg del producto (99 %). EM 244.22 $(M-1)^-$.

Parte B: 2-((S)-1-trans)-4-((terc-butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxilato de metilo: El producto formado en el Ejemplo 37 Parte A (350 mg, 1.4 mmol) se acopló con ácido N-(Boc)-tranexámico de conformidad con el procedimiento descrito por el Ejemplo 2 Parte A para proporcionar 290 mg del producto (43 %). EM 485.22 $(M+H)^+$.

Parte C: 2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxilato de metilo, sal del ácido bistrifluoroacético: El producto formado en el Ejemplo 37 Parte B (290 mg, 0.60 mmol) se trató de conformidad con el procedimiento descrito por el Ejemplo 2 Parte B para proporcionar el compuesto del título (138 mg, 49 %). ^{1}H RMN (500 MHz, d_4-MeOH) δ 1.05 (ddd, J = 12.51, 8.66, 4.12 Hz, 3 H) 1.36 (ddd, J = 29.14, 12.65, 3.30 Hz, 3 H) 1.56 (dd, J = 7.15, 3.85 Hz, 1 H) 1.75 (d, J = 12.10 Hz, 1 H) 1.84 (dd, J = 10.17, 2.47 Hz, 4 H) 2.21 (m, 1 H) 2.63 (d, J = 9.35 Hz, 1 H) 2.76 (d, J = 7.15 Hz, 3 H) 3.24 (dd, J = 7.97, 2.47 Hz, 3 H) 3.88 (s, 4 H) 5.24 (t, J = 7.97

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Hz, 1 H) 7.12 (d, J = 7.15 Hz, 3 H) 7.20 (t, J = 7.15 Hz, 1 H) 7.25 (m, 3 H) 7.86 (s, 1 H); EM 385.33 $(M+H)^+$.

Ejemplo 38

Ácido 2-((S)-1-(trans-4-(Aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxílico, sal del ácido bistrifluoroacético

Parte A: ácido 2-((S)-1-(trans)-4-((terc-butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxílico: El producto del Ejemplo 37 Parte B (290 mg, 0.62 mmol) se disolvió en una solución de MeOH (2 mL) y NaOH 1 N (4 mL) y se agitó para 72 horas a temperatura ambiente. El solvente se evaporó hasta secarse. El residuo se diluyó con agua y se trató con HCl 1 N. La solución resultante se diluyó con EtOAc, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar 138 mg del ácido (49%). EM 471.05 $(M + 1)^+$.

Parte B: ácido 2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxílico, sal del ácido bistrifluoroacético: El producto del Ejemplo 38 Parte A (50 mg, 0.11 mmol) se trató con el TFA de conformidad con el procedimiento descrito por el Ejemplo 2 Parte B. El residuo resultante se volvió a disolver en $MeOH/H_2O$ (9:1) que contiene TFA al 0.1% y se aisló por CLAR

preparativa para proporcionar 17.1 mg del compuesto del título (44%). ^{1}H RMN (500 MHz, d_4-MeOH) δ 0.93 (m, 3 H), 1.24 (m, 3 H), 2.12 (m, 1 H), 2.64 (d, J = 6.87 Hz, 3 H), 2.73 (s, 1 H), 2.86 (s, 1 H), 3.13 (dd, J = 13.75, 8.25 Hz, 1 H), 3.2 (m, 2H), 7.01 (d, J = 6.87 Hz, 3 H), 7.11 (d, J = 7.33 Hz, 1 H), 7.15 (t, J = 7.33 Hz, 3 H), 7.81 (s, 1 H); EMAR $(M + H)^+$ para $C_{20}H_{26}N_4O_3$, m/z calculado: 371.2083, obs: 371.2072.

Ejemplo 39

2-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxamido)acetato de etilo, sal del ácido bistrifluoroacético

Parte A: 2-(2-((S)-1-(trans-4-((terc-butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxamido)acetato de etilo: El producto del Ejemplo 38 Parte A (30.0 mg, 0.06 mmol) y 2-aminoacetato de etilo (10 mg, 0.09mmol) se trataron bajo las condiciones descritas en el Ejemplo 2 Parte A con la substitución de HOBt (10 mg, 0.09 mmol) para the HOAt. El aceite amarillo resultante (33.0. mg, 97% de rendimiento) se llevó a la siguiente etapa sin purificación adicional. EM 556.45 $(M+H)^+$.

Parte B: 2-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-carboxamido)acetato, sal del ácido bistrifluoroacético: El

producto del Ejemplo 39 Parte A (33.0 mg, 0.06 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B. El residuo resultante se volvió a disolver en MeOH/H_2O (9:1) que contiene TFA al 0.1 % y se aisló por CLAR preparativa para proporcionar 2.0 mg del compuesto del título (7%). ^1H RMN (500 MHz, d_4-MeOH) δ 1.03 (m, 3 H), 1.27 (t, J = 7.15 Hz, 4 H), 1.37 (m, 3 H), 1.56 (m, 2 H), 1.72 (d, J = 13.20 Hz, 1 H), 1.83 (dd, J = 8.80, 3.85 Hz, 4 H), 2.20 (m, 1 H), 2.76 (d, J = 7.15 Hz, 3 H), 3.19 (dd, J = 13.75, 8.25 Hz, 1 H), 3.25 (m, 2H), 4.10 (s, 3 H), 4.20 (q, J = 7.15 Hz, 3 H), 5.25 (t, J=7.70 Hz, 1 H), 7.16 (t, J=7.15 Hz, 3 H), 7.19 (d, J=7.15 Hz, 1 H), 7.24 (t, J=7.15 Hz, 3 H), 7.67 (s, 1 H): EMAR $(M + Na)^+$ para $C_{24}H_{33}N_5O_4$, m/z calculado: 478.2403, obs: 478.2453.

Ejemplo 42

2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxilato de metilo, sal de ácido bistrifluoroacético

Parte A: 2-(1-(terc-butoxicarbonil)-2-feniletil)-1H-benzo[d]imidazol-5-carboxilato de (S)-metilo: A una solución de L-N-(Boc)-fenilalanina (265 mg, 1.0 mmol) y el reactivo BOP (464 mg, 1.0 mmol) en piridina (10 mL) se le agregó 3,4-diaminobenzoato de metilo (166 mg, 1.0 mmol). La mezcla de reacción se agitó a 80°C durante 3 días. El solvente se

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removió bajo vacío. El residuo se volvió a disolver en EtOAc. La solución se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse. El producto crudo se purificó por CLAR preparativa para proporcionar 178 mg de la amida (45%). EM 340.2 $(M+H)^+$.

Parte B: 2-(1-amino-2-feniletil)-1H-benzo[d]imidazol-5-carboxilato de (S)-metilo: El producto formado en el Ejemplo 42 Parte A (178 mg, 0.45 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B para proporcionar 180 mg de la amina (76%). EM 296.2 $(M+H)^+$.

Parte C: 2-((S)-1-(trans-4-((terc-butoxicarbonil)metil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxilato de metilo: El producto formado en el Ejemplo 42 Parte B (178 mg, 0,34 mmol) se acopló con ácido N-(Boc)-tranexámico de conformidad con el procedimiento descrito por el Ejemplo 2 Parte A para proporcionar 75 mg del producto deseado (41 %). EM 535.5 $(M+H)^+$.

Parte D: 2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxilato de metilo, sal del ácido bistrifluoroacético: El producto formado en el Ejemplo 42

Parte C (15 mg, 0.028 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 2 Parte B para proporcionar 12 mg del compuesto del título (65 %). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H), 1.52-1.60 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.27-2.29 (m, 1H), 2.77, (d, J = 7.15 Hz, 2H), 3.45 (m, 2H), 3.96 (s, 3H), 5.48 (t, J = 8.25 Hz, 1H), 7.22-7.26 (m, 5H), 7.80 (d, J = 7.0 Hz, 1H), 8.19 (dd, J = 7.0 Hz, 1.2 Hz, 1H), 8.36 (s, 1H); EM 435.3 $(M+H)^+$.

Ejemplo 43

Ácido 2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxílico, sal del ácido bistrifluoroacético

Parte A: ácido 2-((S)-1-(trans-4-((terc-butoxicarbonil)metil)ciclohexanecarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxílico: El compuesto del Ejemplo 42 Parte C (50 mg, 0.093 mmol) se hidrolizó usando las condiciones descritas por el Ejemplo 38 Parte A con la excepción de que el etanol se usó en lugar de metanol proporcionando 38 mg del ácido (78%). EM 521.3 $(M+H)^+$.

Parte B: ácido 2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxílico, sal del ácido

bistrifluoroacético: El compuesto del Ejemplo 43 Parte A (15 mg, 0.029 mmol) se convirtió al producto del título usando el procedimiento descrito por el Ejemplo 2 Parte B (12 mg, 64%). ^{1}H-RMN (400 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.27-2.28 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.43 (d, J = 8.34 Hz, 2H), 5.48 (t, J = 8.12 Hz, 1H), 7.22-7.26 (m, 5H), 7.80 (d, J = 8.78 Hz, 1H), 8.19 (dd, J = 8.35 Hz y 1.3 Hz, 1H), 8.36 (s, 1H); EM 421.2 $(M+H)^+$.

Ejemplo 44

2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxamida, sal del ácido bistrifluoroacético

Parte A: (trans-4-(((S)-1-(5-carbamoil-1H-benzo[d]imidazol-2-il)-2-feniletil)carbamoil)ciclohexil)metilcarbamato de terc-Butilo: El compuesto del Ejemplo 43 Parte A (23 mg, 0.044 mmol) se sometió a las condiciones descritas por el Ejemplo 1 Parte C con la excepción de que el hidróxido de amonio se usó en lugar del clorohidrato del ácido 4-amidinobenzoico para proporcionar 18 mg del producto deseado (79 %). EM 520.0 $(M+H)^+$.

Parte B. 2-((S)-1-(trans-4-

(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-carboxamida, sal del ácido bistrifluoroacético: El compuesto del Ejemplo 44 Parte A (18 mg, 0.034 mmol) se hace reaccionar con TFA siguiendo las condiciones descritas por el Ejemplo 2 Parte B para proporcionar 8 mg del compuesto del título (36%). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.27-2.28 (m, 1H), 2.77 (d, J = 7.14 Hz, 2H), 3.43 (d, J = 7.70 Hz, 2H), 5.48 (t, J = 8.24 Hz, 1H), 7.22-7.27 (m, 5H), 7.80 (d, J = 8.78 Hz, 1H), 8.05 (dd, J = 8.79 Hz, 1.64 Hz, 1H), 8.25 (s, 1H); EM 420.2 $(M+H)^+$.

Ejemplo 45

2-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-il)acetato de etilo, sal del ácido bistrifluoroacético

Parte A: 2-(4-amino-3-nitrofenil)acetato de etilo: A una solución del éster de etilo del ácido 4-(aminofenil)acético (538 mg, 3.0 mmol) en ácido acético (20 mL) se le agregó ácido nítrico (90%, 420 mg, 6 mmol). La mezcla de reacción se agitó a 100°C durante 4 horas. La reacción se enfrió hasta temperatura ambiente. El ácido acético se removió parcialmente bajo vacío. El residuo se diluyó con EtOAc. El pH de la solución se ajustó hasta 8-9 con NaOH al 10%. Se

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lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El producto crudo se aisló por cromatografía en gel de sílice para dar 128 mg (20% de rendimiento) de un sólido amarillo brillante. Se tomó en la siguiente etapa sin purificación adicional.

Parte B. 2-(3,4-diaminofenil)acetato de etilo: A una suspensión de paladio en carbono al 10% (15 mg) en 2 mL de MeOH se agregó a la solución del producto del Ejemplo 45 Parte A (128 mg) en MeOH (8 mL). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 horas. El catalizador se filtró. Al filtrado se le agregó HCl 1 N (0.1 mL) y el solvente se evaporó hasta secarse para proporcionar 130 mg del producto crudo como la sal HCl (86% de rendimiento). EM 195.2 $(M+H)^+$.

Parte C. 2-(2-(1-(terc-butoxicarbonil)-2-feniletil)-1H-benzo[d]imidazol-5-il)acetato de (S)-etilo: El producto del Ejemplo 45 Parte B (130 mg, 0.49 mmol) y L-N-(Boc)-fenilalanina (130 mg, 0.49 mmol) se sometió a las condiciones descritas por el Ejemplo 42 Parte A para proporcionar 210 mg (100% de rendimiento) del producto deseado. EM 424.3 $(M+H)^+$.

Parte D: 2-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-

benzo[d]imidazol-5-il)acetato de etilo, sal del ácido bistrifluoroacético: El producto del Ejemplo 45 Parte C se trató con TFA y luego se acopló con ácido N-(Boc)-tranexámico de conformidad con el procedimiento descrito por el Ejemplo 2 Parte A para proporcionar el producto deseado el cual se hace reaccinar con TFA siguiendo las condiciones descritas por el Ejemplo 2 Parte B para proporcionar el compuesto del título. EM 463.43 $(M+H)^+$. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.24 (t, J = 3.30 Hz, 3 H), 1.35 (m, 2H), 1.56 (m, 1H), 1.78 (br d, J = 12.65 Hz, 1H), 1.86 (m, 3H), 2.28 (m, 1H), 2.77 (d, J = 7.15 Hz, 2H), 3.31 (s, 2H), 3.42 (d, J = 7.70 Hz, 2 H), 3.84 (s, 2 H), 4.16 (q, J = 7.15 Hz, 2H), 5.46 (t, J = 8.25 Hz, 1 H), 7.23 (m, 5 H), 7.51 (d, J = 8.80 Hz, 1H), 7.68 (d, J = 8.80 Hz, 2H); EM 463.4 $(M+H)^+$.

Ejemplo 46

Ácido 2-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-benzo[d]imidazol-5-il)acético, sal del ácido bistrifluoroacético

El producto del Ejemplo 45 Parte D se hidrolizó con LiOH y luego se trató con TFA siguiendo las condiciones descritas por el Ejemplo 2 Parte B para proporcionar el compuesto del título. EM 435.4 $(M+H)^+$. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.35 (m, 2H), 1.55 (m, 1H), 1.78 (br d, J = 12.10 Hz,

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1H), 1.86 (m, 3H), 2.28 (m, 1H), 2.77 (d, J = 6.60 Hz, 2H), 3.31 (s, 2H), 3.42 (d, J = 8.25 Hz, 2 H), 3.82 (s, 2 H), 5.46 (t, J = 8.25 Hz, 1 H), 7.23 (m, 5 H), 7.52 (d, J = 8.24 Hz, 1H), 7.67 (d, J = 8.25 Hz, 2H); EM 435.4 $(M+H)^+$.

Ejemplo 47

trans-N-((S)-1-(5-(2-amino-2-oxoetil)-1H-benzo[d]imidazol-2-il)-2-feniletil)-4-(aminometil)ciclohexancarboxamida, sal del ácido bistrifluoroacético

Este compuesto se preparó a partir del producto del Ejemplo 45 Parte D usando el mismo procedimiento descrito por la síntesis del Ejemplo 44. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.06 (m, 2H), 1.35 (m, 2H), 1.55 (m, 1H), 1.78 (br d, J = 11.86 Hz, 1H), 1.86 (m, 3H), 2.28 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.31 (s,2H), 3.42 (d, J = 8.35 Hz, 2 H), 3.70 (s, 2 H), 5.46 (t, J = 8.35 Hz, 1 H), 7.23 (m, 5 H), 7.52 (d, J = 8.35 Hz, 1H), 7.67 (d, J = 8.325 Hz, 2H); EM 434.3 $(M+H)^+$.

Ejemplo 48

trans-4-(Aminometil)-N-((S)-2-fenil-1-(5-feniloxazol-2-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético

Parte A: (S)-2-(1,3-Dioxo-1,3-dihidro-isoindol-2-il)-N-(2-oxo-2-fenil-etil)-3-fenil-propionamida: N-ftaloil-L-fenilalanina (290 mg, 1 mmol) y 2-aminoacetofenona (171 mg, 1

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mmol) se disolvieron en 10 mL de piridina. El reactivo Bop (470 mg, 1.1 mmol) se agregó. La mezcla se agitó a temperatura ambiente bajo N_2 durante 12 horas. El solvente se removió. El residuo se disolvió en EtOAc y se lavó con agua y $NaHCO_3$ saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró para proporcionar 412 mg del producto (100% de rendimiento). EM 413.2 $(M+H)^+$.

Parte B: (S)-2-(2-fenil-1-(5-feniloxazol-2-il)etil)isoindolin-1,3-diona: El producto del Ejemplo 48 Parte A (412 mg, 1 mmol) se disolvió en DMF y se trató con oxicloruro de fósforo (460 mg, 3 mmol) a 90°C de conformidad con el procedimiento descrito por Robert Dow et al. (J. Org. Chem., 1990, 55, 386) para proporcionar 160 mg (41 % de rendimiento) del producto. EM 395.2 $(M+H)^+$.

Parte C: (S)-2-Fenil-1-(5-feniloxazol-2-il)etanamina: Una solución del producto del Ejemplo 48 Parte B (160mg, 0.4 mmol) en EtOH (10mL) se agregó a hidrazina (39 mg, 1.2 mmol). La mezcla de reacción se puso a reflujo durante 2 horas. Se enfrió hasta temperatura ambiente. El EtOH se removió bajo vacío. El residuo se volvió a disolver en diclorometano. El sólido no disuelto se removió por filtración. El filtrado se concentró para proporcionar 95 mg del producto como un sólido amarillo (90% de rendimiento). EM 265.1 $(M+H)^+$.

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Parte D: trans-4-(Aminometil)-N-((S)-2-fenil-1-(5-feniloxazol-2-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 48 Parte C (95 mg, 0.35 mmol) se convirtió al compuesto del título por aplicación secuencial del procedimiento descrito por el Ejemplo 2 Parte A y Parte B (26%). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.04-1.10 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.22 (m, 1H), 2.77 (d, J = 7.14 Hz, 2H), 3.20 (m, 1H), 3.33 (m, 1H), 5.41 (m, 1H), 7.22-7.27 (m, 5H), 7.34 (1, J = 7.15 Hz, 1H), 7.42 (m, 3H), 7.63-7.65 (d, J = 8.25Hz, 2H); EM 404.3 $(M+H)^+$.

Ejemplo 49

trans-4-(Aminometil)-N-((S)-2-fenil-1-(5-fenil-2H-1,2,4-triazol-3-il)etil)ciclohexan-carboxamida, sal del ácido bistrifluoroacético

Parte A: 2-fenil-1-(5-fenil-2H-1,2,4-triazol-3-il)etilcarbamato de (S)-terc-butilo: La L-N-(Boc)-fenilalanina (265 mg, 1 mmol) e hidrazina (64 mg, 2 mmol) se combinaron usando las condiciones descritas por el Ejemplo 1 Parte C para formar 279 mg de ácido hidrazoico (100% de rendimiento). EM 280.1 $(M+H)^+$. A una solución de ácido hidrazoico (279 mg, 1.0 mmol) y Et_3N (161 mg, 1.6 mmol) en 10 mL de acetonitrilo se le agregó clorohidrato de etilbenzimidato (278 mg, 1.5 mmol). La reacción se calentó

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hasta reflujo durante 24 horas. La reacción se enfrió hasta temperatura ambiente y se diluyó con EtOAc. La mezcla se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse in vacuo. El producto crudo se purificó por CLAR preparativa para proporcionar 154 mg de un aceite (42% de rendimiento). EM 365.2 $(M+H)^+$.

Parte B: trans-4-(aminometil)-N-((S)-2-fenil-1-(5-fenil-2H-1,2,4-triazol-3-il)etil)ciclohexano-carboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 49 Parte A (154 mg, 0.42 mmol) se convirtió al compuesto del título por aplicación secuencial del procedimiento descrito por el Ejemplo 1 Parte B, Ejemplo 2 Parte A y Parte B (28%). ^{1}H-RMN (400 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.29-1.42 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.83-1.86 (m, 3H), 2.21 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.18-3.21 (m, 1H), 3.31 (m, 1H), 5.42 (t, J = 8.12 Hz, 1H), 7.22-7.26 (m, 5H), 7.51-7.52 (m, 3H), 7.96-7.98 (m, 2H); EM 404.2 $(M+H)^+$.

Ejemplo 50 trans-4-(Aminometil)-N-((S)-2-fenil-1-(3-fenil-1H-pirazol-5-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético

Parte A: ácido 3-oxo-3-fenilpropanoico: A una solución de acetato de etil benzoilo (2.88g, 15 mmol) en EtOH (30 mL) se le agregó NaOH 1N (30 mL). La mezcla de reacción se agitó

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a temperatura ambiente durante 72 horas. Se enfrió hasta 0°C y se hizo ácido con HCl 1 N. El EtOH se removió bajo presión reducida. La capa acuosa se extrajo dos veces con diclorometano. La solución de diclorometano combinada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró in vacuo para dar un sólido amarillo ligero (600 mg, 24%). EM 165.1 $(M+H)^+$.

Parte B: 3,5-dioxo-1,5-difenilpentan-2-il carbamato de (S)-bencilo: A una solución del producto del Ejemplo 50 Parte A (600mg, 3.65 mmol) en THF (20 mL) y MeOH (20 mL) se le agregó etóxido de magnesio (417mg, 3.65 mmol). La mezcla se agitó a temperatura ambiente durante 4 horas. Los solventes se removieron bajo presión reducida. El producto crudo se disolvió en DMF (2 mL) y se agregó a una mezcla de N-CBZ-L-fenilalanina (800mg, 2.68mmol), 1,1'-carbonildiimidazol (520mg, 3.21mmol) en DMF (4 mL) la cual se agitó durante 2 horas a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante la noche. Se diluyó con EtOAc, se lavó con HCl diluido, agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró in vacuo. El producto crudo se purificó por CLAR preparativa para dar el producto (140 mg, 13%). EM 402.1 $(M+H)^+$.

Parte C: 2-fenil-1-(3-fenil-1H-pirazol-5-

il)etilcarbamato de (S)-bencilo: A una solución del Ejemplo 50 Parte B (32mg, 0.08mmol) en EtOH (3mL) se le agregó hidrato de hidrazina (3 mg, 0.09 mmol). La mezcla de reacción se calentó a 60°C durante 3 horas. El EtOH se removió in vacuo para dar el producto deseado (0.32 mg, 100%). EM 398.1 $(M+H)^+$.

Parte D: (S)-2-Fenil-1-(3-fenil-1H-pirazol-5-il)etanamina: A una solución del Ejemplo 50 Parte C en MeOH (3 mL) se le agregó Pd/C al 10% (5 mg). La mezcla de reacción se agitó bajo H_2 a temperatura ambiente durante 4 horas. El catalizador se removió por filtración. La mezcla cruda se purificó por CLAR preparativa para dar el producto deseado (12mg, 57%). EM 262.2 $(M-H)^-$.

Parte E: trans-4-(Aminometil)-N-((S)-2-fenil-1-(3-fenil-1H-pirazol-5-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 50 Parte D (12 mg, 0.046 mmol) se convirtió al compuesto del título por aplicación secuencial del procedimiento descrito por el Ejemplo 2 Parte A y Parte B (11 mg,46%). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.30-1.33 (m, 1H), 1.43-1.46 (m, 1H), 1.56 (m, 1H), 1.64 (m, 1H), 1.83 (m, 3H), 2.16-2.18 (m, 1H), 2.75 (d, J = 7.03 Hz, 2H), 3.08-3.10 (m, 1H), 3.27 (m, 1H), 5.35 (t, J = 8.12 Hz, 1H), 6.61 (s, 1H), 7.22 (m, 1H),

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7.23 (m, 4H), 7.35-7.36 (t, J = 7.15Hz, 1H), 7.41-7.44 (t, J = 7.70Hz, 2H), 7.69-7.71 (d, J = 7.15 Hz, 2H); EM 403.1 $(M+H)^+$.

Ejemplo 51

trans-4-(aminometil)-N-((S)-1-(5-oxo-1-fenil-4,5-dihidro-1H-1,2,4-triazol-3-il)-2-feniletil)-ciclohexancarboxamida, sal del ácido bistrifluoroacético

Parte A: 1-(5-oxo-1-fenil-4,5-dihidro-1H-1,2,4-triazol-3-il)-2-feniletilcarbamato de (S)-bencilo: Una solución de (S)-N-CBZ-fenilalanina nitrilo (140 mg, 0.5 mmol) y metóxido de sodio (13 mg, 0.24 mmol) en MeOH (4mL) se agitó a 30°C durante 3 horas. El ácido acético (1mg, 0.2mmol) se agregó, seguido por fenil hidrazina (108 mg, 1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se enfrió hasta 0°C, y el sólido se removió por filtración. La solución de MeOH se purificó por cromatografía en gel de sílice para dar un aceite amarillo, el cual se disolvió en THF (6 mL) y el 1,1'-carbonildiimidazol (68 mg, 0.42 mmol) se agregó. La mezcla se calentó hasta reflujo durante 48 horas. La reacción se enfrió hasta temperatura ambiente, se diluyó con CH_2Cl_2, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró in vacuo para dar 38 mg (66%) del producto como un sólido rojo. EM 413.2 $(M-H)^-$.

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Parte B: Trans-4-(aminometil)-N-((S)-1-(5-oxo-1-fenil-4,5-dihidro-1H-1,2,4-triazol-3-il)-2-feniletil)-ciclohexancarboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 51 Parte A (38 mg, 0.09 mmol) se convirtió al compuesto del título por aplicación secuencial del procedimiento descrito por el Ejemplo 50 Parte D, y Ejemplo 2 Parte A y Parte B (8 mg, 17%). ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.30-1.33 (m, 1H), 1.43-1.46 (m, 1H), 1.56 (m, 1H), 1.67 (m, 1H), 1.81-1.86 (m, 3H), 2.16-2.18 (m, 1H), 2.75 (d, J = 7.15 Hz, 2H), 3.08-3.10 (m, 1H), 3.31 (m, 1H), 5.15-5.17 (m, 1H), 7.19-7.21 (m, 2H), 7.27-7.28 (m,4H), 7.40-7.43 (t, J = 7.97Hz, 2H), 7.85-7.87 (d, J = 7.69Hz, 2H); EM 420.1 $(M+H)^+$.

Ejemplo 52

trans-4-(aminometil)-N-((S)-2-fenil-1-(2-fenil-1H-imidazol-4-il)etil)ciclohexan-carboxamida, sal del ácido bistrifluoroacético

Parte A: 2-fenil-1-(2-fenil-1H-imidazol-4-il)etilcarbamato de (S)-bencilo: Una solución de (S)-bencil-4-bromo-3-oxo-1-fenilbutan-2-il carbamato (376 mg, 1.0 mmol) y formiato de sodio (68 mg, 1.0 mmol) en EtOH (15 mL) se calentó hasta reflujo durante 14 horas. La benzamidina (240 mg, 1.5 mmol) y bicarbonato de sodio (400 mg, 4.7 mmol) se agregaron a la reacción. La mezcla de reacción se calentó

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hasta reflujo durante 24 horas adicionales. La reacción se enfrió hasta temperatura ambiente y se secó in vacuo. El residuo se volvió a disolver en EtOAc, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró in vacuo. El producto crudo se purificó por cromatografía en gel de sílice para proporcionar 33 mg (8% de rendimiento). EM 398.1 $(M+H)^+$.

Parte B: Trans-4-(aminometil)-N-((S)-2-fenil-1-(2-fenil-1H-imidazol-4-il)etil)ciclohexan-carboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 52 Parte A (33 mg, 0.083 mmol) se convirtió al compuesto del título por aplicación secuencial del procedimiento descrito por el Ejemplo 50 Parte D, y Ejemplo 2 Parte A y Parte B (5 mg,12% de rendimiento). ^{1}H-RMN (400 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.30-1.33 (m, 1H), 1.43-1.46 (m, 1H), 1.56 (m, 1H), 1.67 (m, 1H), 1.83 (m, 3H), 2.16-2.18 (m, 1H), 2.75 (d, J = 7.03 Hz, 2H), 3.08-3.10 (m, 1H), 3.31 (m, 1H), 5.34-5.36 (m, 1H), 7.22-7.29 (m, 5H), 7.51 (s, 1H), 7.62-7.68 (m, 3H), 7.87-7.89 (m, 2H); EM 403.3 $(M+H)^+$.

Ejemplo 53

N-(4-carbamimidoilfenil)-3-fenil-2-(4-fenil-1H-imidazol-2-il)propanamida, sal del ácido bis-trifluoroacético

Parte A: ácido 2-bencil-3-metoxi-3-oxopropanoico: El

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ácido bencil malónico (19.4 g, 0.10 mol) se disolvió en 180 mL de MeOH. La mezcla se enfrió en un baño de hielo y se le agregó cloruro de tionilo gota a gota durante 30 minutos (7.3 mL, 0.10 mol). La mezcla se agitó en el baño de hielo durante 30 minutos y luego a temperatura ambiente durante 30 minutos bajo N_2. El solvente se removió, y el residuo se disolvió en $NaHCO_3$ acuoso. La solución básica se extrajo con EtOAc para remover el bis-éster el cual se descartó. La solución acuosa luego se hizo ácido con HCl acuoso hasta pH 5 y se extrajo con EtOAc. El extracto de EtOAc se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró para dar 7.2 g de ácido 2-bencil-3-metoxi-3-oxopropanoico (35%). EM 209.24 $(M+H)^+$.

Parte B: 3-fenil-2-(4-fenil-1H-imidazol-2-il)propanoato de metilo: El producto del Ejemplo 53 Parte A (1.04 g, 5.0 mmol) se disolvió en EtOH (13 mL) y una solución de Cs_2CO_3 (0.81 g, 2.5 mmol) en H_2O (13 mL) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora bajo N_2. El solvente se removió bajo vacío, y la sal resultante se suspendió en DMF (20 mL). La 2-bromoacetofenona (1.3 g, 6.6 mmol) se agregó en una porción sencilla, y la reacción se agitó a temperatura ambiente bajo N_2 durante 2 horas. La reacción se filtró para remover el CsBr. Los sólidos se lavaron con DMF. Los lavados combinados y el filtrado se concentraron in vacuo para proporcionar un sólido amarillo.

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El intermediario crudo se colocó en un matraz equipado con una trampa Dean-Stark y se disolvió en xileno (40 mL). El NH_4OAc (7.78 g, 100 mmol) se agregó al matraz y la reacción se calentó hasta reflujo durante 3 horas. La reacción se enfrió hasta temperatura ambiente y el solvente se removió in vacuo. El residuo se volvió a disolver en EtOAc y se lavó con $NaHCO_3$ acuoso saturado y salmuera, se secó sobre Na_2SO_4, se filtró, se concentró, y se purificó por cromatografía instantánea (gel de sílice, EtOAc/hexano) para proporcionar 600 mg del producto deseado (39%). EM 307.29 $(M+H)^+$.

Parte C: ácido 3-Fenil-2-(4-fenil-1H-imidazol-2-il)propanoico: El producto del Ejemplo 53 Parte B (350 mg, 1.14 mmol) se disolvió en 9 mL de EtOH y NaOH 1N (3 mL) se agregó. La mezcla se agitó a temperatura ambiente bajo N_2 durante 30 minutos. El HCl acuoso se agregó a la mezcla de reacción hasta un pH 5. El precipitado formado se filtró y se secó para proporcionar 284 mg del producto deseado (85%). EM 293.33 $(M+H)^+$.

Parte D: sal bis-TFA de N-(4-carbamimidoilfenil)-3-fenil-2-(4-fenil-1H-imidazol-2-il)propanamida: El producto del Ejemplo 53 de la Parte C (40 mg, 0.14 mmol) y clorohidrato de 4-amidinobenzamidina (48 mg, 0.16 mmol) se disolvieron en piridina anhidra (2 mL). El reactivo BOP (90 mg, 0.16 mmol) se agregó y la reacción se agitó a temperatura

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ambiente bajo N_2 durante 48 horas. El solvente se removió in vacuo. El residuo se volvió a disolver en CH_3OH/H_2O (9:1) que contiene TFA al 0.1%, y se purificó por CLAR de fase inversa (C18, 28x100 mm, MeOH/H_2O/0.1%TFA gradiente) para proporcionar 15 mg del compuesto del título (17% de rendimiento). ^{1}H-RMN (400 MHz, d_4-MeOH) δ 3.33 (dd, J = 13.40, 9.45 Hz, 1 H), 3.52 (dd, J = 13.62, 7.03 Hz, 1 H),4.54 (dd, J = 9.23, 7.03 Hz, 1 H), 7.12 (m, 5 H), 7.39 (m, 3 H), 7.57 (d, J = 6.59 Hz, 2 H), 7.70 (m, 3 H), 7.76 (m, 2 H). EMAR (M + H)$^+$ para $C_{25}H_{24}N_5O$, m/z calculado: 410.1981, obs: 410.2001.

Ejemplo 54

N-(3-Carbamimidoilfenil)-3-fenil-2-(4-fenil-1H-imidazol-2-il)propanamida, sal del ácido bis-trifluoroacético

El compuesto del título se preparó usando el mismo procedimiento descrito por el Ejemplo 53. RMN (400 MHz, d_4-MeOH) δ 3.42 (dd, J = 13.62, 9.23 Hz, 1 H), 3.61 (dd, J = 13.62, 7.03 Hz, 1 H), 4.61 (dd, J = 9.01, 7.25 Hz, 1 H), 7.24 (m, 5 H), 7.51 (m, 5 H), 7.66 (d, J = 7.91 Hz, 2 H), 7.77 (m, 2 H), 8.19 (s, 1 H); EM 410.20, $(M+H)^+$.

Ejemplo 55

trans-N-(4-(aminometil)ciclohexil)-3-fenil-2-(4-fenil-1H-imidazol-2-il)propanamida, sal del ácido bistrifluoroacético

Parte A: (trans-4-aminociclohexil)metilcarbamato de

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bencilo: el trans-4-aminometilciclohexilcarbamato de t-butilo (344 mg, 1.5 mmol) se disolvió en CH_2Cl_2 (7 mL) y se enfrió en un baño de hielo. La trietilamina (0.21 mL, 1.5 mmol) se agregó, seguido por cloroformiato de bencilo (0.22 mL, 1.5 mmol) gota a gota. La mezcla se agitó a temperatura ambiente bajo N_2 durante 2 horas. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró hasta un sólido blanco. Este sólido se disolvió en 10 mL de HCl-dioxano 4 N y se agitó a temperatura ambiente durante 10 minutos El solvente se removió. El residuo se secó bajo vacío para dar 350 mg del producto deseado como un sólido blanco (78%). EM 263.36 $(M+H)^+$.

Parte B: (trans-4-(3-fenil-2-(4-fenil-1H-imidazol-2-il)propanamido)ciclohexil)metilcarbamato de bencilo: El producto del Ejemplo 55 Parte A (75 mg, 0.25 mmol) y el producto del Ejemplo 53 Parte C (60 mg, 0.21 mmol) se disolvieron en piridina anhidra (5 mL). El reactivo BOP (115 mg, 0.26 mmol) se agregó y la reacción se agitó a temperatura ambiente bajo N_2 durante 4 horas. El solvente se removió in vacuo. El residuo se volvió a disolver en EtOAc, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se concentró y se purificó por cromatografía instantánea (EtOAc/hexano) para proporcionar 50 mg del producto deseado (44%). EM 537.32 $(M+H)^+$.

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Parte C: N-(trans-4-(aminometil)ciclohexil)-3-fenil-2-(4-fenil-1H-imidazol-2-il)propanamida, sal del ácido bis-trifluoroacético: El producto del Ejemplo 55 Parte B (50 mg, 0.093 mmol) se disolvió en MeOH (8 mL) y una cantidad catalítica de Pd/C al 10% se agregó. La mezcla se colocó bajo 1 atmósfera de H_2 durante 4 horas. Se filtró a través de celite y se lavó con MeOH. El filtrado se concentró y se purificó por CLAR de fase inversa para dar 33 mg del compuesto del título (56%). ^{1}H-RMN (400 MHz, d_4-MeOH) δ 0.92-1.22 (m, 4 H), 1.59 (m, 1 H), 1.70-1.88 (m, 4 H), 2.69 (m, 2 H), 3.21 (m, 1 H), 3.35 (m, 1 H), 3.50 (m, 1 H), 4.32 (t, J = 8.35 Hz, 1 H), 7.12-7.32 (m, 5 H), 7.38-7.54 (m, 3 H), 7.66 (d, J = 7.03 Hz, 2 H), 7.75 (s, 1 H). EM 403.39 $(M+H)^+$.

Ejemplo 56

4-(2-(1-(4-carbamimidoilfenilamino)-1-oxo-3-fenilpropan-2-il)-1H-imidazol-4-il)benzamida, sal del ácido bis-trifluoroacético

Parte A: 2-(4-(4-cianofenil)-1H-imidazol-2-il)-3-fenilpropanoato de metilo: El ácido 2-bencil-3-metoxi-3-oxopropanoico del Ejemplo 53 Parte A (5.0 g, 24.0 mmol) se disolvió en EtOH (40 mL) y una solución de Cs_2CO_3 (4.0 g, 12.0 mmol) en H_2O (40 mL) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora bajo N_2. El

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solvente se removió bajo vacío y la sal resultante se suspendió en DMF (85 mL). El 4-(2-bromoacetil)benzonitrilo (5.4 g, 24.0 mmol) se agregó en una porción sencilla y la reacción se agitó a temperatura ambiente bajo N_2 durante 4 horas. La reacción se filtró para remover CsBr. Los sólidos se lavaron con DMF. Los lavados combinados y el filtrado se concentraron in vacuo para proporcionar un sólido amarillo. El intermediario crudo se colocó en un matraz equipado con una trampa Dean-Stark y se disolvió en xileno (200 mL). El NH_4OAc (38.9 g, 500 mmol) se agregó al matraz y la reacción se calentó hasta reflujo durante 3 horas. La reacción se enfrió hasta temperatura ambiente y el solvente se removió in vacuo. El residuo se volvió a disolver en EtOAc y se lavó con $NaHCO_3$ acuoso saturado y salmuera, se secó sobre Na_2SO_4, se filtró, se concentró, y se purificó por cromatografía instantánea (gel de sílice, EtOAc/ hexano) para proporcionar 2.4 g del producto deseado (30%). EM 332.27 $(M+H)^+$.

Parte B: ácido 2-(4-(4-carbamoilfenil)-1H-imidazol-2-il)-3-fenilpropanoico: El producto del Ejemplo 56 Parte A (0.99 g, 3.0 mmol) se disolvió en 10 mL de DMSO. El carbonato de potasio (1.24 g, 9.0 mmol) se agregó. La mezcla se enfrió hasta 0-5°C y el H_2O_2 al 30% (3.18 mL de solución acuosa al 30%) se agregó, seguido por óxido de magnesio (0.24 g, 15 mmol). El baño de enfriamiento se removió y la mezcla se

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agitó a temperatura ambiente bajo N_2 durante 4 horas. La mezcla se filtró para remover el material inorgánico. El agua (30 mL) se agregó al filtrado y la mezcla resultante se agitó a temperatura ambiente durante 40 minutos. La mezcla se hizo ácida con HCl 1N hasta pH 5. El precipitado formado se filtró y se secó para proporcionar 0.67 g del ácido (67%). EM 336.30 $(M+H)^+$.

Parte C: 4-(2-(1-(4-Carbamimidoilfenilamino)-1-oxo-3-fenilpropan-2-il)-1H-imidazol-4-il)benzamida, sal del ácido bis-trifluoroacético: El ácido del Ejemplo 56 Parte B (55 mg, 0.16 mmol) y clorohidrato de 4-amidinobenzamidina (58 mg, 0.34 mmol) se disolvieron en piridina anhidra (3 mL). El reactivo BOP (108 mg, 0.24 mmol) se agregó y la reacción se agitó a temperatura ambiente bajo N_2 durante 48 horas. El solvente se removió in vacuo. El residuo se volvió a disolver en CH_3OH/H_2O (9:1) que contiene TFA al 0.1%, y se purificó por CLAR de fase inversa ($MeOH/H_2O$/0.1%TFA gradiente) para proporcionar 11 mg del compuesto del título (10%). ^{1}H-RMN (400 MHz, d_4-MeOH) δ 3.34 (m, 1 H), 3.49 (m, 1 H), 4.29 (t, J = 7.91 Hz, 1 H), 7.17 (m, 1 H), 7.22 (m, 4 H), 7.56 (s, 1 H), 7.78 (m, 6 H), 7.89 (m, 2 H). EMAR $(M + H)^+$ para $C_{26}H_{25}N_6O_2$, m/z calculado: 453.2039, obs: 453.2025.

Ejemplo 57

4-(2-(1-(1-Aminoisoquinolin-6-ilamino)-1-oxo-3-fenilpropan-2-il)-1H-imidazol-4-il)benzamida, sal del ácido bis-trifluoroacético

El ácido 2-(4-(4-carbamoilfenil)-1H-imidazol-2-il)-3-fenilpropanoico del Ejemplo 56 Parte B (36 mg, 0.11 mmol) y 6-aminoisoquinolin-1-ilcarbamato de terc-butilo (18 mg, 0.050 mmol) se disolvieron en piridina anhidra (3 mL). El reactivo BOP (50 mg, 0.11 mmol) se agregó y la reacción se agitó a 60°C bajo N_2 durante 3 horas, y luego a temperatura ambiente durante 48 horas. El solvente se removió in vacuo. El residuo se volvió a disolver en EtOAc (1 mL) y HCl-dioxano 4N (1 mL) y se agitó a temperatura ambiente durante 1.5 hora. La mezcla se concentró y luego se volvió a disolver en CH_3OH/H_2O (9:1) que contiene TFA al 0.1%, y se purificó por CLAR de fase inversa ($MeOH/H_2O$/0.1 % TFA gradiente) para proporcionar 6.0 mg del compuesto del título (17%). ^{1}H-RMN (400 MHz, MeOH-d_4) δ 3.45 (m, 1 H), 3.63 (m, 1 H), 4.62 (dd, J = 7.03 Hz, 1 H), 7.14 (d, J = 7.03 Hz, 1 H), 7.26 (m, 5 H), 7.53 (d, J = 7.03 Hz, 1 H), 7.79 (d, J = 8.35 Hz, 2H), 7.85 (dd, J = 9.23, 2.20 Hz, 1H), 7.90 (s, 1 H), 7.99 (d, J = 8.35 Hz, 2H), 8.33 (d, J = 1.76 Hz, 1H), 8.38 (d, J = 8.79 Hz, 1H). EM 477.3 $(M + H)^+$.

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Ejemplo 58

4-(2-(1-(isoquinolin-6-ilamino)-1-oxo-3-fenilpropan-2-il)-1H-imidazol-4-il)benzamida, sal del ácido bis-trifluoroacético

El compuesto del título se preparó usando el mismo método descrito en el Ejemplo 57. EM 462.19 $(M + H)^+$. ^{1}H-RMN (400 MHz, MeOH-d_4) δ 3.36 (d, J = 7.47 Hz, 1 H), 3.51 (d, J = 8.35 Hz, 1H), 4.31 (t, J = 7.91 Hz, 1 H), 7.15 (m, 1 H), 7.23 (d, J = 6.59 Hz, 4H), 7.54 (s, 1 H), 7.65 (dd, J = 8.79, 2.20 Hz, 2H), 7.74 (d, J = 6.15 Hz, 1H), 7.80 (d, J = 8.79 Hz, 2 H), 7.89 (m, 2H), 8.03 (d, J = 9.23 Hz, 1H), 8.35 (m, 1H), 9.10 (s, 1 H).

Ejemplo 59

4-(2-(4-(4-carbamimidoilfenil)-1H-imidazol-2-il)-3-fenilpropanamido)benzamida, sal del ácido bis-trifluoroacético

Parte A: ácido 2-(4-(4-cianofenil)-1H-imidazol-2-il)-3-fenilpropanoico: El 2-(4-(4-cianofenil)-1H-imidazol-2-il)-3-fenilpropanoato de metilo del Ejemplo 56 Parte A (60 mg, 0.20 mmol) se disolvió en 4 mL de EtOH. El NaOH (1.5 mL de solución acuosa 1 N) se agregó y la mezcla se agitó a temperatura ambiente durante 1.5 hora. La mezcla se hizo ácida con HCl 1N hasta pH 5. El precipitado formado se filtró y se secó para dar 40 mg del ácido (63%). EM 318.3 $(M+H)^+$.

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Parte B: 4-(2-(4-(4-Cianofenil)-1H-imidazol-2-il)-3-fenilpropanamido)benzamida: El ácido del Ejemplo 59 Parte A (100 mg, 0.32 mmol), trietilamina (150 µL, 1.2 mmol), y el reactivo BOP (210 mg, 0.48 mmol) se disolvieron en THF (9 mL). La mezcla se agitó a temperatura ambiente durante 15 minutos y la 4-aminobenzamida (47 mg, 0.35 mmol) se agregó. La mezcla resultante se calentó a 70°C bajo N_2 durante 1 hora. La mezcla se concentró y luego se volvió a disolver en EtOAc. Se lavó con agua y salmuera, se secó sobre Na_2SO_4, se concentró, y se purificó por cromatografía instantánea (gel de sílice, EtOAc/hexano) para dar 45 mg del producto deseado (32%). EM 436.3 $(M+H)^+$.

Parte C: 4-(2-(4-(4-Carbamimidoilfenil)-1H-imidazol-2-il)-3-fenilpropanamido)benzamida, sal del ácido bis-trifluoroacético: El clorohidrato de hidroxilamina (72 mg, 1.0 mmol) se disolvió en DMSO (1 mL) y la trietilamina (0.14 mL, 10 eq) se agregó. La mezcla se agitó durante 5 minutos y el precipitado se filtró completamente. El filtrado se agregó al producto del Ejemplo 59 Parte B (28 mg, 0.064 mmol) y la mezcla se agitó a temperatura ambiente durante 15 minutos, luego la 4-aminobenzamida (47 mg, 0.35 mmol) se agregó. La mezcla resultante se calentó a 65°C bajo N_2 durante 1.5 hora. Se enfrió y el agua se agregó. El precipitado formado se filtró y se secó. El sólido luego se disolvió en CH_2Cl_2 (3 mL) y el anhídrido acético (13 µL) se agregó. La mezcla se agitó

a temperatura ambiente bajo N_2 durante 1.5 hora. El CH_2Cl_2 se removió y el residuo se disolvió en MeOH-HOAc (3 mL de solución 10:1). El Pd/C (10%, 18 mg) se agregó y la mezcla se colocó bajo un globo de hidrógeno durante 3 horas. Se filtró a través de Celite, se concentró, luego se volvió a disolver en CH_3OH/H_2O (9:1) que contiene TFA al 0.1%, y se purificó por CLAR inversa ($MeOH/H_2O$/0.1%TFA gradiente) para proporcionar 8.0 mg del compuesto del título (18%). ^{1}H-RMN (400 MHz, MeOH-d_4) δ 3.37 (m, 1H), 3.45 (m, 1 H), 4.24 (t, J = 7.91 Hz, 1 H), 7.16 (m, 1 H), 7.22 (m, 4 H), 7.62 (d, J=8.79 Hz,3H), 7.80 (m,4H), 7.94 (d,J= 8.79, 2 H). EM 453.4 $(M + H)^+$.

Ejemplo 60

4-(2-(1-(4-Carbamimidoilbencilamino)-1-oxo-3-fenilpropan-2-il)-1H-imidazol-4-il)benzamida, sal del ácido bis-trifluoroacético

El ácido del Ejemplo 56 Parte B se acopló con 4-cianobencilamina siguiendo el procedimiento del Ejemplo 59 Parte B. El grupo ciano luego se convirtió a la correspondiente benzamidina usando los procedimientos del Ejemplo 59 Parte C. EM 467.22 $(M + H)^+$. ^{1}H-RMN (400 MHz, MeOH-d_4) δ 3.37 (dd, J = 13.62, 8.35 Hz, 1H), 3.53 (m, 1 H), 4.37 (d, J= 15.82 Hz, 1 H), 4.55 (m, 2 H), 7.22 (m, 2 H), 7.29 (m, 5 H), 7.71 (d, J= 8.35 Hz, 2 H), 7.79 (d, J= 8.79 Hz, 2 H), 7.91 (s, 1 H), 7.99 (d, J = 8.35 Hz, 2H).

Ejemplo 61

N-(4-Carbamimidoilfenil)-4-fenil-3-(4-fenil-1H-imidazol-2-il)butanamida, sal del ácido bis-trifluoroacético

Este compuesto se preparó siguiendo el mismo procedimiento descrito en el Ejemplo 53 usando el ácido 2-bencilsucínico como el material de partida. EM 424.21 $(M + H)^+$. ^{1}H-RMN (400 MHz, MeOH-d_4) δ 3.107 (d, J = 3.95 Hz, 1H), 3.15 (m, 1 H), 3.25 (dd, J= 13.40, 6.37 Hz, 1 H), 3.95 (m, 1 H), 7.12 (d, J = 6.95 Hz, 2 H), 7.25 (m, 3 H), 7.46 (m, 3 H), 7.61 (d, J= 7.03 Hz, 2 H), 7.69 (s, 1 H), 7.75 (m, 4 H).

Ejemplo 62

4-(Aminometil)-N-((S)-1-(4-(3-metoxifenil)-1H-imidazol-2-il)-2-feniletil)ciclohexan-carboxamida, sal del ácido bistrifluoroacético

Parte A: 1-(1H-imidazol-2-il)-2-feniletilcarbamato de (S)-terc-butilo: El 1-oxo-3-fenilpropan-2-il carbamato de (S)-terc-butilo (5.08 g, 20.4 mmol) y dihidrato glioxal trimérico (2.2 g, 10.1 mmol) se disolvieron en MeOH anhidro (30 mL). El amoniaco en metanol (2.0 M, 45.6 mL, 92.4 mmol) se agregó y la reacción se agitó durante 48 horas a temperatura ambiente. El solvente se removió bajo vacío. El aceite resultante se diluyó con EtOAc, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó in vacuo para proporcionar 1.4 g (47%) de sólido blanco. EM 288.15 $(M+H)^+$.

Parte B: 1-(4,5-dibromo-1H-imidazol-2-il)-2-feniletilcarbamato de (S)-terc-butilo: El producto del Ejemplo 62 Parte A (510 mg, 1.8 mmol) se disolvió en cloroformo (10 mL) y se trató con NBS (600 mg, 3.38 mmol) a temperatura ambiente. La reacción se agitó durante 1 hora. El solvente se removió bajo vacío y el producto crudo se purificó usando cromatografía en gel de sílice para proporcionar 510 mg (64%) de un sólido blanco EM 445.91 $(M+H)^+$.

Parte C: 1-(4-bromo-1H-imidazol-2-il)-2-feniletilcarbamato de (S)-terc-butilo: El producto del Ejemplo 62 Parte B (821 mg, 2.38 mmol) se disolvió en una mezcla de 1,4 dioxanos (8 ml) y agua (2 mL). El sulfito de sodio (3.00g, 23.8 mmol) y sulfato ácido de tetrabutilamonio (2.01 g, 5.95 mmol) se agregaron. La reacción se calentó a 100°C durante 48 horas. La reacción se diluyó con EtOAc y los sólidos se filtraron completamente. El filtrado se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse. El crudo se purificó por cromatografía en gel de sílice para proporcionar 200 mg (24%) de un sólido blanco EM 366.3 $(M + H)^+$.

Parte D. (S)-1-(4-bromo-1H-imidazol-2-il)-2-feniletanamina: El producto del Ejemplo 62 Parte C (560 mg,

1.53 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B para proporcionar 490 mg del producto crudo como un aceite amarillo que contiene TFA en exceso. El producto crudo se usó en la siguiente reacción sin purificación adicional. EM 268.3 $(M + H)^+$.

Parte E: ((1S,4r)-4-(((S)-1-(4-bromo-1H-imidazol-2-il)-2-feniletil)carbamoil)ciclohexil)metilcarbamato de terc-butilo: El producto del Ejemplo 62 Parte D (494 mg, 1.86 mmol) y ácido N-Boc-tranexámico (480 mg, 1.8 mmol) se trataron usando las condiciones descritas en el Ejemplo 2 Parte A. El sólido blanco resultante (780 mg, 83 %) se llevó a la siguiente etapa sin purificación adicional. EM 503.28 $(M+H)^-$.

Parte F. ((1S,4r)-4-(((S)-1-(4-(3-metoxifenil)-1H-imidazol-2-il)-2-feniletil)carbamoil)ciclohexil-metilcarbamato de terc-butilo: El producto del Ejemplo 62 Parte E (30.0 mg, 0.059 mmol) se pesó en un vial que contiene ácido 3-metoxifenil borónico (11 mg, 0.07 mmol) y K_3PO_4 (38 mg, 0.177 mmol). Los sólidos se disolvieron en 1,4 dioxanos (0.5 mL). El dímero de bromuro de paladio (I) tri terc-butil fosfina (19 mg, 0.024 mmol) se agregó, y el vial se selló bajo argón. La reacción se calentó usando irradiación de microondas a 110°C durante 1 hora. La reacción se enfrió

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hasta temperatura ambiente, y los sólidos se filtraron completamente. El filtrado se colectó y se secó bajo vacío. El producto crudo, contaminado con material de partida, se llevó a la siguiente etapa. EM 433.22 $(M + H)^+$.

Parte G: 4-(Aminometil)-N-((S)-1-(4-(3-metoxifenil)-1H-imidazol-2-il)-2-feniletil)ciclohexan-carboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 62 Parte F (30 mg, 0.059 mmol) se trató con TFA de conformidad con el procedimiento descrito por el Ejemplo 1 Parte B. El producto se aisló por CLAR preparativa para proporcionar 6.00 mg (24%) como el compuesto del título. ^1H RMN (500 MHz, d_4-MeOH) δ 1.07 (m, 2 H) 1.16 (dd, J = 12.37, 3.57 Hz, 1 H) 1.27 (d, J = 15.40 Hz, 1 H) 1.39 (m, 2 H) 1.57 (m, 2 H) 1.80 (d, J = 12.10 Hz, 1 H) 1.86 (d, J = 11.00 Hz, 3 H) 1.94 (d, J = 11.00 Hz, 1 H) 2.26 (m, 2 H) 2.77 (d, J = 7.15 Hz, 2 H) 2.83 (d, J = 7.15 Hz, 1 H) 3.37 (m, 1 H) 3.78 (s, 1 H) 3.85 (s, 3 H) 5.30 (t, J = 8.25 Hz, 1 H) 6.63 (m, 1 H) 6.81 (m, 1 H) 6.81 (m, 1 H) 7.19 (m, 4 H) 7.24 (t, J = 7.42 Hz, 1 H) 7.28 (m, 3 H) 7.39 (m, 1 H) 7.76 (s, 1 H): EM 433.22 $(M + H)^+$.

Los Ejemplos 63-65 y 89 enlistados en la Tabla 2 se sintetizaron similarmente por la aplicación apropiada del procedimiento descrito por el Ejemplo 62 o por la extensión directa de aquellos procedimientos por alguien experto en el arte.

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Ejemplo 66

Ácido trans-3-(2-((S)-1-(4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidaz 1-4-il)-benzoico, sal del ácido bistrifluoroacético

El producto del Ejemplo 7 (85 mg, 0.18 mmol) se hidrolizó de conformidad con el procedimiento descrito por el Ejemplo 26. El producto crudo se volvió a disolver en MeOH/H_2O (9:1) que contiene TFA al 0.1% y se evaporó hasta secarse para proporcionar 86 mg (71%) del compuesto del título. ^1H RMN (500 MHz, $CDCl_3$) δ 0.92 (m, 2 H), 1.18 (m, 2 H), 1.48 (m, 1 H), 1.64 (d, J = 12.60 Hz, 1 H), 1.77 (d, J = 11.00 Hz, 3 H), 2.15 (t, J = 12.10 Hz, 1 H), 2.61 (m, 2 H), 3.23 (m, 1 H), 3.42 (m, J = 5.50 Hz, 1 H), 5.37 (bs, 1 H), 7.21 (t, J = 6.32 Hz, 1 H), 7.27 (m, 3 H), 7.63 (t, J = 7.42 Hz, 1 H), 8.00 (m, 3 H), 8.15 (d, J = 6.60 Hz, 1 H), 8.39 (s, 1 H); EMAR $(M + H)^+$ para $C_{26}H_{30}N_4O_3$, m/z calculado: 447.2396, obs: 447.2407.

Ejemplos 67 y 68

4-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)benzoato de metilo, sal del ácido bis-trifluoroacético (67) y ácido 4-(2-((S)-1-(trans-4-(aminometil)ciclohexan-carboxamido)-2-feniletil)-1H-imidaz 1-4-il)benzoico, sal del ácido bis-trifluoroacético (68)

Parte A: 4-(2-(1-(terc-butoxicarbonil)-2-feniletil)-1H-

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imidazol-4-il)benzoato de (S)-etilo: El producto (8.5 g, 97% durante dos etapas) se sintetizó a partir de L-N-(Boc)-fenilalanina (3.99 g, 20 mmol), Cs_2CO_3 (3.25 g, 10 mg), 4-(2-bromoacetil)benzoato de etilo (5.4 g, 20 mmol) y acetato de amonio (31 g, 400 mmol) por la aplicación apropiada de las condiciones descritas por el Ejemplo 1 Parte A. EM 436.1 $(M + 1)^+$.

Parte B: 4-(2-((S)-1-(trans-4-(aminometil)ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)benzoato de etilo, sal del ácido bistrifluoroacético: El producto de la Parte A (220 mg, 0.48 mmol) se trató secuencialmente de conformidad con el procedimiento por el Ejemplo 1 Parte B, y Ejemplo 2 Parte A y Parte B para proporcionar 200 mg del producto (56% durante tres etapas). EM 334.2 (M-H)-.

Parte C: Ejemplo 67 y 68: El producto de la Parte B (200 mg, 0.28 mmol) se disolvió en MeOH/H_2O (9:1) que contiene TFA al 0.1% (2 mL). El pH de la solución se ajustó hasta 12-14 usando NaOH acuoso 1 N. La reacción se agitó a temperatura ambiente durante 16 horas. El TFA se agregó a la solución hasta que alcanzó pH = 1 y los productos se aislaron por CLAR preparativa para proporcionar 66 mg del Ejemplo 67 (34%) y 34 mg del Ejemplo 68 (18%).

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Datos para el Ejemplo 67: ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.06 (m, 2H), 1.38 (m, 2 H), 1.57 (m, 1 H), 1.80 (d, J = 11.55 Hz, 1 H), 1.86 (d, J = 11.55 Hz, 3 H), 2.28 (tt, J = 12.10, 3.30 Hz, 1 H), 2.77 (d, J = 6.60 Hz, 2 H), 3.33 (d, J = 8.25 Hz, 1 H), 3.38 (dd, J = 13.20, 8.00 Hz, 1 H), 3.93 (s, 3 H), 5.33 (t, J = 8.25 Hz, 1 H), 7.18 (d, J = 7.15 Hz, 2 H), 7.23 (t, J = 7.15 Hz, 1 H), 7.29 (t, J = 7.15 Hz, 2 H), 7.77 (d, J = 8.80 Hz, 2 H), 7.89 (s, 1 H), 8.11 (d, J=8.80 Hz, 2 H); EMAR $(M + H)^+$ para $C_{27}H_{32}N_4O_3$, m/z calculado: 461.2523, obs: 461.2570.

Datos para el Ejemplo 68: ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.06 (m, 2 H), 1.39 (m, 2 H), 1.57 (m, 1 H), 1.80 (d, J = 12.10 Hz, 1 H), 1.86 (d, J = 11.55 Hz, 3 H), 2.28 (tt, J = 12.10, 3.30 Hz, 1 H), 2.77 (d, J = 7.15 Hz, 2 H), 3.33 (d, J = 8.25 Hz, 1 H), 3.39 (dd, J = 13.50, 8.25 Hz, 1 H), 5.33 (t, J = 8.25 Hz, 1 H), 7.19 (d, J = 7.15 Hz, 2 H), 7.24 (t, J = 7.15 Hz, 1 H), 7.29 (t, J = 7.15 Hz, 2 H), 7.76 (d, J = 8.25 Hz, 2 H), 7.89 (s, 1 H), 8.12 (d, J = 8.80 Hz, 2 H); EMAR $(M+H)^+$ para $C_{26}H_{30}N_4O_3$, m/z calculado: 447.2396, obs: 447.2397.

Ejemplo 69

trans-N-((S)-1-(4-(3-Amino-1H-indazol-6-il)-1H-imidazol-2-il)-2-feniletil)-4-(aminometil)-ciclohexancarboxamida, sal del ácido bistrifluoroacético

El producto del Ejemplo 65 (10 mg, 0.022 mmol) se

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disolvió en 1-butanol. La hidrazina (66 mg, 1.32 mmol) se agregó y la mezcla de reacción se calentó hasta 118°C usando irradiación de microondas en un tubo sellado para 4.5 horas. La reacción se enfrió hasta temperatura ambiente y se agitó durante 8 horas adicionales. El solvente y el exceso de hidrazina se removieron in vacuo. El producto se volvió a disolver en $MeOH/H_2O$ (9:1) que contiene TFA al 0.1%. El solvente se removió bajo vacío para proporcionar el compuesto del título (8.8 mg, 59%). EMAR $(M + H)^+$ para $C_{26}H_{31}N_7O$, m/z calculado: 458.2668, obs: 458.2650.

Ejemplo 70

trans-4-(aminometil)-N-bencil-N-((S)-2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético

Parte A: (S)-N-Bencil-2-fenil-1-(4-fenil-1H-imidazol-2-il)etanamina: El producto del Ejemplo 1 Parte B (33 mg, 0.1 mmol) y benzaldehído (16 mg, 0.15 mmol) se disolvieron en CH_2Cl_2 (4 mL). El $NaBH(OAc)_3$ (32 mg, 0.15 mmol) se agregó, seguido por algunas gotas de HOAc. La reacción se agitó a temperatura ambiente durante 48 horas. La reacción se diluyó con CH_2Cl_2 y se lavó con agua y salmuera. Se secó sobre Na_2SO_4, se filtró y se evaporó in vacuo para dar 42 mg, del producto crudo. EM 354.5 $(M+H)^+$.

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Parte B: trans-4-(Aminometil)-N-bencil-N-((S)-2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)ciclohexancarboxamida, sal del ácido bistrifluoroacético: El producto del Ejemplo 70 Parte A se convirtió al compuesto del título siguiendo el mismo procedimiento descrito en el Ejemplo 2 Parte A-B. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 0.95 (m, 2 H), 1.25 (m, 1H), 1.60 (m, 3 H), 1.80 (m, 3 H), 2.49 (t, J = 8.52 Hz, 1H), 2.72 (d, J = 7.15 Hz, 2H), 3.53 (d, J = 3.30 Hz, 2 H), 4.80 (m, 2 H), 6.14 (t, J = 8.25 Hz, 1 H), 7.00-7.53 (m, 16 H). EM 493.20 $(M + H)^+$.

Los Ejemplos 71-74 y el Ejemplo 85 enlistados en la Tabla 5 se sintetizaron por la aplicación apropiada del procedimiento descrito por el Ejemplo 70 o por la extensión directa del procedimiento descrito por el Ejemplo 70 por alguien experto en el arte.

Ejemplo 77

[2-fenil-1-(4-fenil-1H-imidazol-2-il)-etil]-amida del ácido trans-4-aminometil-ciclohexanocarboxílico, sal del ácido bistrifluoroacético

Parte A: éster de fenilo del ácido {4-[2-Fenil-1-(4-fenil-1H-imidazol-2-il)-etilcarbamoil]-ciclohexil-metil-carbámico

El producto del Ejemplo 55 Parte A (36 mg, 0.1 mmol) se disolvió en THF/DMF (2:1, 6 mL) y se enfrió hasta 0°C. La diciclohexil-carbodiimida (162 mg, 0.1 mmol) se agregó a la

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solución. La mezcla resultante se agitó a 0°C durante 1 hora. El producto del Ejemplo 1 Parte B (33 mg, 0.1 mmol) se agregó, y la reacción se entibió hasta 50°C durante 5 horas. La reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc, se lavó con agua y salmuera (3X), se secó sobre Na_2SO_4, se filtró, y se secó in vacuo. El compuesto del título se aisló por CLAR preparativa para proporcionar 27 mg (40%) como un sólido incoloro EM 552.1 $(M+H)^+$.

Parte B: [2-fenil-1-(4-fenil-1H-imidazol-2-il)-etil]-amida del ácido 4-aminometil-ciclohexanocarboxílico: El producto del Ejemplo 77 Parte A (27 mg mg, 0.04 mmol) se convirtió al producto final (16 mg, 75%) usando el procedimiento descrito por el Ejemplo 50 Parte C. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.09 (m, 2 H), 1.19 (m, 2H), 1.57 (m, 1H), 1.81 (m,2H) 1.92 (m, 2H), 2.76 (d, J = 6.60 Hz, 2H), 3.25 (m, 1H), 3.35 (m, 2H), 5.21 (t, J = 7.42 Hz, 1H), 7.16 (d, J = 7.15 Hz, 2H), 7.24-7.29 (m, 3H), 7.44-7.49 (m, 3H), 7.65 (d, J = 8.24 Hz, 2H), 7.72 (s, 1H). EM 418.1 $(M+1)^+$.

Ejemplo 82

(S)-4-[2-[1-[4-(aminometil)ciclohexancarboxamido]amino]-2-feniletil]-4-(bromo-1H-imidazol-5-il)-benzamida

Parte A: éster de terc-butilo del ácido (4-[1-[5-bromo-4-(4-carbamoil-fenil)-1H-imidazol-2-il]-2-fenil-

etilcarbamoil)-ciclohexilmetil)-carbámico: El producto del Ejemplo 28 Parte A (70 mg, 0.13 mmol) se disolvió en $CHCl_3$ (10 mL) y se trató con bromo (21 mg, 0.13 mmol). Después de agitar durante 16 horas, la reacción se evaporó hasta secarse in vacuo para proporcionar 93 mg (>99%) del producto. EM 625.3/627.3 (1:1; $M+H)^+$.

Parte B. 4-(2-(1-[(4-Aminometil-ciclohexanocarbonil)-amino]-2-fenil-etil)-5-bromo-1H-imidazol-4-il)-benzamida: El producto crudo del Ejemplo 82 Parte A (93 mg, 0.13 mmol) se convirtió al compuesto del título (35.8 mg, 36%) usando el procedimiento descrito por el Ejemplo 2 Parte B. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 1.38 (m, 1 H) 1.57 (m, 1 H) 1.76 (d, J = 12.65 Hz, 1 H) 1.85 (d, J = 9.90 Hz, 3 H) 2.23 (dt, J = 12.10, 3.30 Hz, 1 H) 2.77 (d, J = 7.15 Hz, 2 H) 3.20 (dd, J = 13.20, 8.25 Hz, 1 H) 3.26 (dd, J = 13.30, 7.70 Hz, 1 H) 5.23 (t, J = 7.97 Hz, 1 H) 7.17 (d, J = 7.15 Hz, 2 H) 7.21 (d, J = 7.15 Hz, 1 H) 7.26 (t, J = 7.15 Hz, 2 H) 7.75 (d, J = 8.80 Hz, 2 H) 7.95 (d, J = 8.80 Hz, 2 H). EM 524.3/526.3 (1:1; $M+H)^+$.

Ejemplo 107

(S)-4-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-feniletil]-4-(trifluorometil)-1H-imidazol-5-il]-benzamida, sal del ácido bis-trifluoroacético

Parte A: éster de terc-butilo del ácido trans-(4-[(S)-1-

(4-Bromo-5-trifluorometil-1H-imidazol-2-il)-2-fenil-etilcarbamoil]-ciclohexilmetil)-carbámico: El producto de la Parte A del Ejemplo 32 se convirtió al compuesto del título por la aplicación secuencial del procedimiento descrito por el Ejemplo 1 Parte B, Ejemplo 2 Parte A y Ejemplo 82 Parte A. EM: 573.3/575.3 $(M+1)^+$.

Parte B: éster de terc-butilo del ácido trans-(4-{(S)-1-[4-(4-carbamoil-fenil)-5-trifluorometil-1H-imidazol-2-il]-2-fenil-etilcarbamoil)-ciclohexilmetil)-carbámico: El producto del Ejemplo 107 Parte A (47 mg, 0.069 mmol), ácido 4-carbamoilfenil-borónico (30 mg, 0.18 mmol), K_3PO_4 (75 mg, 0.35 mmol), y $Pd(PPh_3)_4$ (22 mg) se agregaron junto con 6 mL de 1,4-dioxano. La mezcla se calentó en un tubo sellado en el microondas a 110°C durante 1.5 hora. El solvente se removió. El residuo se disolvió en EtOAc y se lavó con agua y salmuera. Se secó sobre $MgSO_4$, se concentró, y se purificó por cromatografía instantánea (sílice, EtOAc/hexano) para dar 25 mg del producto deseado. EM: 614.4 $(M+1)^+$.

Parte C: trans-4-(2-{(S)-1-[(4-Aminometil-ciclohexanocarbonil)-amino]-2-fenil-etil}-5-trifluorometil-1H-imidazol-4-il)-benzamida, sal del ácido bis-trifluoroacético: El producto del Ejemplo 107 Parte B se convirtió al Ejemplo 107 (15 mg) por la aplicación apropiada

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del procedimiento descrito por el Ejemplo 2 Parte B. EM: 514.3 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.04 (m, 2H), 1.39 (m, 2H), 1.57 (m, 1H), 1.82 (m, 4H), 2.21 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.20 (m, 2H), 5.25 (m, 1H), 7.20 (m, 5H), 7.50 (d, J = 8.35 Hz, 2H), 7.93 (d, J = 8.79 Hz, 2H).

Ejemplo 108

N-{(S)-1-[4-(4-Carbamimidoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-benzamida

El clorohidrato de hidroxilamina (10 eq) se disolvió en DMSO (1 mL) y se agregó trietilamina (10 eq). La mezcla se agitó durante 5 minutos, luego se filtró para remover el clorohidrato de trietilamina. El compuesto del Ejemplo 178 Parte A (80 mg) se agregó al filtrado y la mezcla se calentó a 65°C durante 1-1.5 hora. La reacción se enfrió hasta temperatura ambiente, se diluyó con ~10 mL agua, y el precipitado resultante se colectó, se lavó con agua y se secó para dar el intermediario de amidoxima (73 mg, 84%). m/z 426.4 $(M+H)^+$. Este material se suspendió en cloruro de metileno (10 mL) y anhídrido acético (0.040 mL) se agregó. La mezcla se agitó durante 20 minutos a temperatura ambiente bajo argón luego se evaporó hasta secarse. El residuo se disolvió en una mezcla de metanol/HOAc (10:1), el Pd/C al 10% se agregó y la mezcla se agitó bajo 1 atmósfera de H_2 durante 2 horas. El catalizador se removió por filtración, el

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filtrado se evaporó y el residuo se purificó por CLAR C18 preparativa para proporcionar la sal bis TFA del compuesto del título (65 mg, 60%) ^{1}H RMN (400 MHz, MeOH-D4) δ 3.41-3.59 (m, 2 H) 5.53 (t, J=8.13 Hz, 1 H) 7.20-7.31 (m, 5 H) 7.46 (t, J=7.69 Hz, 2 H) 7.56 (t, J=7.47 Hz, 1 H) 7.84 (d, J=7.03 Hz, 2 H) 7.87 - 7.95 (m, 5 H) m/z 410.2 $(M+H)^+$.

Ejemplo 109

Ácido trans-5-(2-{(S)-1-[(4-aminometil-ciclohexanocarbonil)-amino]-2-fenil-etil}-1H-imidazol-4-il)-2-ciano-benzoico, sal del ácido bistrifluoroacético

Parte A: éster de metilo del ácido 5-acetil-2-ciano-benzoico: El anhídrido tríflico (10 g, 35.4 mmol) se agregó gota a gota a una solución enfriada (-40°C) de éster de metilo del ácido 5-acetil-2-hidroxi-benzoico (6.9 g, 35.4 mmol) y DIPEA (5.3 g, 42.5 mmol) en CH_2Cl_2 (100 mL). La reacción se entibió hasta -10°C y se agitó durante 16 horas. La reacción se entibió hasta temperatura ambiente, se evaporó hasta secarse in vacuo, y se volvió a disolver en EtOAc. La capa orgánica se lavó con salmuera 1/2 saturada, se secó sobre $MgSO_4$, se filtró y se evaporó in vacuo. Una proción del triflato crudo (5.01 g, 15.3 mmol) se disolvió en DMF (40 mL). El tetraquis(trifenilfosfina) paladio (0) (1.3 g, 1.1 mmol) y cianuro de zinc (2.16 g, 18.4 mmol) se agregaron al matraz, y la mezcla se calentó hasta 90°C durante 2.5 horas.

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La reacción se enfrió hasta temperatura ambiente y se agitó con una solución 1:1 de NH_4OH concentrado y agua (160 mL). La suspensión resultante se extrajo con ETOAc. Los extractos orgánicos combinados se lavaron con salmuera 1/2 saturada, se secaron sobre $MgSO_4$, se filtraron y se evaporaron in vacuo. El compuesto del título se aisló por cromatografía en SiO_2 para proporcionar 439 mg (14%) de un sólido blanco EM 221.1 $(M+NH_4)^+$.

Parte B: éster de metilo del ácido 5-(2-Bromo-acetil)-2-ciano-benzoico: El producto del Ejemplo 109 Parte A (107 mg, 0.53 mmol) se disolvió en CH_2Cl_2 (5 mL) y se trató con bromo (84 mg, 0.53 mmol). La solución cambió de color desde color rojizo hasta amarillo después de 3 horas, lo que indica que la reacción se completó. La reacción se diluyó con CH_2Cl_2, se lavó con $NaHCO_3$ saturado, se secó sobre Na_2SO_4, se filtró y se evaporó in vacuo para proporcionar 160 mg (>99%) de un sólido incoloro. ^1H RMN (500 MHz, $CDCl_3$) δ 4.05 (s, 3 H) 4.47 (s, 2 H) 7.97 (d, J = 7.70 Hz, 1 H) 8.26 (m, 1 H) 8.69 (s, 1 H).

Parte C: ácido (S)-2-{[4-(terc-butoxicarbonilamino-metil)-ciclohexanocarbonil]-amino}-3-fenil-propiónico: El ácido 4-(terc-butoxicarbonilamino-metil)-ciclohexanocarboxílico (1.7 g, 6.6 mmol) y clorohidrato de etil fenilalanina (2.0 g, 6.6 mmol) se disolvieron en DMF (30

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mL) y se combinaron con HOAt (0.5 M en DMF, 16 mL, 8 mmol) y 4-metilmorfolina (2.33 g, 23 mmol). A esta mezcla se le agregó EDCI (1.76 g, 9.2 mmol). La reacción se agitó a temperatura ambiente durante 12 horas, se diluyó con EtOAc, se lavó varias veces con salmuera 1/2 saturada, se secó sobre $MgSO_4$, se filtró y se evaporó in vacuo para proporcionar 2.8 g (99%) de un sólido incoloro el cual se disolvió en MeOH (30 mL) y se trató con NaOH 1 N (19 mL) a temperatura ambiente durante 3 horas. El MeOH se removió in vacuo y el residuo se volvió a disolver en agua. La solución acuosa se hizo ácida con HCl 1 N hasta pH 1 y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron in vacuo para proporcionar 2.5 g (95%) del compuesto del título como el ácido libre. EM 403.0 (M+H+).

Parte D: éster de etilo del ácido 5-[2-((S)-1-[[4-(terc-butoxicarbonilamino-metil)-ciclohexanocarbonil]-amino]-2-fenil-etil)-1H-imidazol-4-il]-2-ciano-benzoico: El producto del Ejemplo 109 Parte B (149 mg, 0.53 mmol) y el producto del Ejemplo 109 Parte D (214 mg, 0.53 mmol) se combinaron de conformidad con el procedimiento descrito por el Ejemplo 1 Parte A para proporcionar 73.6 mg (24%) del compuesto del título. EM 584.4 $(M-H^+)^-$.

Parte E: ácido 5-(2-[(S)-1-[(4-aminometil-

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ciclohexanocarbonil)-amino]-2-fenil-etil]-1H-imidazol-4-il)-2-ciano-benzoico: El producto del Ejemplo 109 Parte B (149 mg, 0.53 mmol) y el producto del Ejemplo 109 Parte D (214 mg, 0.53 mmol) se combinaron de conformidad con el procedimiento descrito por el Ejemplo 1 Parte A para proporcionar 73.6 mg (24%) del compuesto del título. EM 584.4 $(M-H^+)^-$.

Parte F: ácido 5-(2-{(S)-1-[(4-aminometil-ciclohexanocarbonil)-amino]-2-fenil-etil]-1H-imidazol-4-il)-2-ciano-benzoico: El producto del Ejemplo 109 Parte E (13 mg, 0.022 mmol) se disolvió en MeOH anhidro y se enfrió hasta 0°C. Se burbujeó gas de amoniaco anhidro en la solución por ca. 15 min, luego el recipiente de reacción se tapó herméticamente y la reacción se agitó durante 24 horas a temperatura ambiente. La reacción se burbujeó con nitrógeno y se evaporó hasta secarse. El producto crudo se disolvió en TFA al 10% en CH_2Cl_2 (v/v) y se agitó durante 16 horas a temperatura ambiente. El solvente y el TFA se evaporaron in vacuo. El producto crudo se volvió a disolver en MeOH/H_2O (9:1) que contiene TFA al 0.1%. El compuesto del título se aisló como un vidrio incoloro por medio de CLAR preparativa para proporcionar 2.0 mg (19%). ^1H RMN (500 MHz, d_4-MeOH) δ 1.06 (m, 2 H) 1.39 (m, 2 H) 1.57 (m, 1 H) 1.79 (d, J = 12.10 Hz, 1 H) 1.86 (d, J = 12.10 Hz, 3H) 2.26 (m, 1 H) 2.77 (d, J = 6.60 Hz, 2 H) 3.33 (d, J = 8.25 Hz, 2 H) 5.32 (t, J = 7.97

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Hz, 1 H) 7.19 (d, J = 6.60 Hz, 2 H) 7.22 (m, 1 H) 7.28 (t, J = 7.15 Hz, 3 H) 7.92 (s, 2 H) 8.09 (d, J = 7.70 Hz, 1 H) 8.13 (s, 1 H). EM 472.3 $(M+H^+)^+$.

Ejemplo 113

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-bromo-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-trans-ciclohexancarboxamida, sal del ácido bis-trifluoroacético

El Ejemplo 113 se sintetizó por la aplicación apropiada del procedimiento descrito en el Ejemplo 120, excepto que el procedimiento del Ejemplo 82 Parte A se uso en lugar del procedimiento del Ejemplo 120 Parte D. ^{1}H RMN (500 MHz, d_4-MeOH) δ 1.05 (m, 2 H) 1.39 (m, 2 H) 1.57 (m, 1 H) 1.75 (bd, J=12.10 Hz, 1 H) 1.85 (bd, J=13.20 Hz, 3 H) 2.22 (m, 1 H) 2.77 (d, J=7.15 Hz, 2 H) 3.16 (dd, J=13.20, 8.25 Hz, 1 H) 3.24 (dd, J=13.20, 7.40 Hz, 1 H) 5.21 (t, J=7.97 Hz, 1 H) 7.18 (m, 3 H) 7.25 (t, J=7.42 Hz, 2 H) 7.47 (d, J=9.90 Hz, 1 H) 7.70 (s, 1 H) 7.92 (d, J=8.25 Hz, 1 H). EM: 536 (M+H+)+.

Ejemplo 114

éster de metilo del ácido (S)-5-[4-(carbamoilfenil]-2-[1-[4-(aminometil)ciclohexancarboxamido]-2-feniletil]-1H-imidazol-4-carboxílico, sal del ácido bis-trifluoroacético

Parte A: éster de metilo del ácido 2-((S)-1-terc-butoxicarbonilamino-2-fenil-etil)-3H-imidazol-4-carboxílico:

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El compuesto de la Parte B del Ejemplo 32 (0.42 g, 1.07 mmol) se disolvió en MeOH (8 mL) y el TFA (0.8 mL) se agregó. La mezcla se agitó a temperatura ambiente bajo N_2 durante 30 minutos. El $NaHCO_3$ acuoso se agregó y el MeOH se removió. El acuoso se extrajo con CH_2Cl_2. La solución de CH_2Cl_2 se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró hasta una espuma amarilla (0.40 g). CL/EM: 346.4 $(M+1)^+$.

Parte B: éster de metilo del ácido 5-bromo-2-((S)-1-terc-butoxicarbonilamino-2-fenil-etil)-3H-imidazol-4-carboxílico: El producto del Ejemplo 114 Parte A (1.2 g de 83% pureza, 0.28 mmol) se disolvió en $CHCl_3$ (20 mL) y el NBS (0.93 g, 0.41 mmol) se agregó. La mezcla se agitó a temperatura ambiente bajo N_2 durante 1.5 hora. Se diluyó con $CHCl_3$ y se lavó con agua y salmuera. Luego se secó sobre $MgSO_4$ y se concentró hasta un sólido blanco (0.79 g). EM: 424.4/426.2 $(M+1)^+$.

Parte C: éster de metilo del ácido trans-5-bromo-2-((S)-1-{(4-(terc-butoxicarbonilamino-metil)-ciclohexanocarbonil]-amino)-2-fenil-etil)-3H-imidazol-4-carboxílico: El producto del Ejemplo 114 Parte B se convirtió al compuesto del título por aplicación secuencial del procedimiento descrito por el Ejemplo 1 Parte B y Ejemplo 2 Parte A. CL/EM: 563.3 $(M+1)^+$.

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Parte D: éster de metilo del ácido trans-2-{(S)-1-[(4-aminometil-ciclohexanocarbonil)-amino]-2-fenil-etil}-5-(4-carbamoil-fenil)-3H-imidazol-4-carboxílico, sal del ácido bis-trifluoroacético: El producto del Ejemplo 114 Parte C se convirtió al Ejemplo 114 por aplicación secuencial del procedimiento descrito por el Ejemplo 107 Parte B y Ejemplo 2 Parte B. EM: 504.4 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.39 (m, 2H), 1.57 (m, 1H), 1.81 (m, 4H), 2.23 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.24 (m, 2H), 3.82 (s, 3H), 5.28 (t, J = 7.91 Hz, 1H), 7.21 (m, 5H), 7.76 (d, J = 8.35 Hz, 2H), 7.94 (d, J = 8.35 Hz, 2H).

Ejemplo 117

(S)-N-[1-[4-[4-(carbamoil)fenil]-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-benzamida

Este compuesto se preparó por la aplicación apropiada del método descrito en el Ejemplo 28. EM: 440.2 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.53 (m, 2H), 4.19 (s, 2H), 5.55 (m, 1H), 7.27 (m, 5H), 7.57 (m, 2H), 7.77 (m, 2H), 7.80-8.02 (m, 5H).

Ejemplo 118

4-Aminometil-N-{(S)-1-[4-(4-carbamoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-2-fluoro-benzamida

Ejemplo 118 se preparó por la aplicación apropiada del

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método descrito en el Ejemplo 28. EM: 458.2 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.47 (dd, J = 13.84 y 8.13 Hz, 2H), 4.18 (s, 2H), 5.59 (t, J = 7.91 Hz, 1H), 7.29 (m, 7H), 7.77 (m, 3H), 7.89 (s, 1H), 7.98 (d, J = 8.79 Hz, 2H).

Ejemplo 119

Ácido trans-2-{(S)-1-[(4-Aminometil-ciclohexanocarbonil)-amino]-2-fenil-etil}-5-(4-carboxi-fenil)-3H-imidazol-4-carboxílico, sal del ácido bis-trifluoroacético

El producto del Ejemplo 114 se hidrolizó con LiOH/THF para dar el Ejemplo 119. EM: 491.4 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.05 (dd, J = 12.52 y 4.17 Hz, 2H), 1.39 (m, 2H), 1.57 (m, 1H), 1.85 (m, 4H), 2.23 (m, 1H), 2.77 (d, J = 7.03 Hz, 2H), 3.23 (m, 2H), 5.29 (t, J = 7.91 Hz, 1H), 7.21 (m, 5H), 7.81 (d, J = 8.35 Hz, 2H), 8.06 (d, J = 8.79 Hz, 2H).

Ejemplo 120

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-trans-ciclohexanocarboxamida, sal del ácido bis-trifluoroacético

Parte A: Ácido 4-ciano-3-fluorobenzoico: Ácido 4-Bromo-3-fluorobenzoico (7.5 g, 0.034 mol), $Zn(CN)_2$ (4.0 g, 0.034 mol) y $Pd(PPh_3)_4$ (3.95 g, 0.0034 mol) se agregaron junto con 60 mL de DMF (desgasificado). La mezcla se calentó a 90°C bajo N_2 durante 3 horas. Esto se enfrió hasta temperatura

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ambiente y se filtró para remover sales inorgánicas insolubles (descartadas). El filtrado se diluyó con agua y se extrajo con EtOAc. La mezcla EtOAc se lavó con agua, salmuera, se secó sobre $MgSO_4$, y se concentró para proporcionar 4.5 g del producto deseado con 90% de pureza. Este material se tomó dentro de la siguiente etapa sin purificación adicional. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 7.82 (m, 1H), 7.90 (m, 3H), 7.56 (d, J = 10.0 Hz, 1H), 7.68 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H).

Parte B: 4-(2-Bromoacetil)-2-fluorobenzonitrilo: El ácido 4-ciano-3-fluorobenzoico (4.0 g de 90% material puro, 0.02 mol) se disolvió en CH_2Cl_2 (50 mL). A esto se le agregó gota a gota cloruro de oxalilo durante 15 minutos (2.3 mL, 0.026 mol). La mezcla se agitó a temperatura ambiente durante 1 hora y luego se calentó a reflujo durante 1 hora bajo N_2. El solvente se removió, y el residuo se volvió a disolver en CH_3CN (50 mL). Esta solución se enfrió hasta -15°C, y a esto se agregó (trimetilsilil)diazometano (11.5 mL de 2.0 M en hexano) gota a gota durante 20 minutos. La mezcla resultante se agitó a -15°C durante 1 hora bajo N_2. A esto se le agregó gota a gota una solución de HBr en HOAc (4.25 mL de 33% en peso) durante 20 minutos, y la mezcla de reacción se agitó a -15°C durante 20 minutos. El solvente se removió, y el residuo se disolvió en EtOAc, se lavó con agua, salmuera, se

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secó sobre $MgSO_4$, y se concentró hasta 3.2 g del producto deseado. EM: 240.1, 242.1, $(M+H)^+$. ^1H-RMN (400 MHz, d_4-MeOH) δ 2.42 (s, 2H), 7.76-7.85 (m, 3H).

Parte C: (S)-1-(4-(4-ciano-3-fluorofenil)-1H-imidazol-2-il)-2-feniletilcarbamato de terc-butilo: El 4-(2-bromoacetil)-2-fluorobenzonitrilo (3.2 g 0.013 mol), L-Boc-fenilalanina (3.5 g, 0.013 mol), y Cs_2CO_3 (2.6 g, 0.008 mol) se agregaron junto con DMF (20 mL). La mezcla se agitó a 15°C durante 1 hora bajo N_2. Se diluyó con 100 mL de EtOAc, se lavó con agua, salmuera, se secó sobre $MgSO_4$, se concentró, y se purificó por cromatografía instantánea (120 g x 2 sílice, 10-55% EtOAc en hexano) para dar 3.5 g del éster deseado. CL/EM: 425.3. Este material luego se combinó con acetato de amonio (12 g) y se suspendió en xileno (100 mL). La mezcla se calentó bajo N_2 a 150°C durante 2.5 horas en un matraz equipado con una trampa Dean-Stark. Los xilenos se removieron. El residuo se disolvió en EtOAc, y se lavó con agua y salmuera. Se secó sobre $MgSO_4$, se concentró, y se purificó por cromatografía instantánea (120 g x 2 sílice, 15-70% EtOAc en hexano) para dar 2.2 g del imidazol deseado. EM: 407 $(M+H)^+$. ^1H-RMN (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.30 (m, 2H), 4.86 (d, J = 6.59 Hz, 1H), 5.32 (d, J = 7.47 Hz, 1H), 7.14-7.24 (m, 6H), 7.53-7.61 (m, 3H).

Parte D: (S)-1-(5-cloro-4-(4-ciano-3-fluorofenil)-1H-imidazol-2-il)-2-feniletilcarbamato de terc-butilo: El producto del Ejemplo 120 Parte C (2.2 g, 5.4 mmol) y N-clorosuccinimida (0.80 g, 6.7 mmol) se agregaron junto con CH_3CN (100 mL). La mezcla se calentó a reflujo durante 7 horas bajo N_2. El solvente se removió, y el residuo se disolvió en EtOAc. Se lavó con agua, $NaHCO_3$ acuoso, y salmuera, se secó sobre $MgSO_4$, y se concentró para dar 2.4 g de espuma. EM: 441.3, $(M+H)^+$. ^{1}H-RMN (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 3.23 (m, 2H), 4.89 (m, 1H), 5.46 (d, J = 7.03 Hz, 1H), 7.07 (d, J = 6.15 Hz, 2H), 7.25-7.26 (m, 5H), 7.54 (m, 1H).

Parte E: 4-(2-((S)-1-amino-2-feniletil)-5-cloro-1H-imidazol-4-il)-2-fluorobenzonitrilo: El producto del Ejemplo 120 Parte D (0.20 g, 0.45 mmol) se agitó con CH_2Cl_2 (6 mL) y TFA (1.5 mL) bajo N_2 durante 0.5 hora. Los solventes se removieron. El residuo se secó bajo vacío para dar 0.26 g de la sal bis-TFA. EM: 340.94, $(M+H)^+$. ^{1}H-RMN (400 MHz, d_4-MeOH) δ 3.33 (m, 2H), 4.56 (dd, J = 8.57, 6.37 Hz, 1H), 7.12 (d, J = 6.59 Hz, 2H), 7.25-7.30 (m, 3H), 7.67 (m, 2H), 7.81 (m, 1H).

Parte F: éster de terc-butilo del ácido trans-(4-[(S)-1-[5-cloro-4-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-2-

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fenil-etilcarbamoil}-ciclohexilmetil)-carbámico: El ácido Boc-tranexámico (0.14 g, 0.54 mmol), reactivo BOP (0.24 g, 0.54 mmol) y TEA (0.38 mL, 2.7 mmol) se agregaron junto con 10 mL de THF. La mezcla se agitó a temperatura ambiente durante 15 minutos bajo N_2, y el producto del Ejemplo 120 Parte E (0.26 g, 0.45 mmol) se agregó. La mezcla resultante se calentó a 75°C durante 15 minutos bajo N_2. La mezcla de reacción se enfrió hasta temperatura ambiente y el solvente se removió. El residuo se disolvió en EtOAc y se lavó con agua y salmuera. Se secó sobre $MgSO_4$, se concentró, y se purificó por cromatografía instantánea (40 g sílice, 10-100% EtOAc en hexano) para dar 0.21 g del producto deseado. EM: 580.3, $(M+H)^+$. ^{1}H-RMN (400 MHz, d_4-MeOH) δ 0.94 (m, 2H), 1.25-1.37 (m, 4H), 1.42 (s, 9H), 1.76-1.79 (m, 3H), 2.15 (m, 1H), 2.85 (m, 2H), 3.20-3.30 (m, 2H), 5.17 (m, 1H), 7.16-7.23 (m, 5H), 7.67-7.80 (m, 3H).

Parte G: {(S)-1-[5-cloro-4-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-2-fenil-etil}-amida del ácido trans-4-aminometil-ciclohexanocarboxílico: El producto del Ejemplo 120 Parte F (0.21 g, 0.36 mmol) se agitó con CH_2Cl_2 (8 mL) y TFA (2 mL) bajo N_2 durante 0.5 hora. Los solventes se removieron. El residuo se secó bajo vacío para dar 0.25 g de la sal bis-TFA. EM: 480.3, $(M+H)^+$.

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Parte H: {(S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-amida del ácido trans-4-aminometil-ciclohexanocarboxílico, sal del ácido bistrifluoroacético: El producto del Ejemplo 120 Parte G (0.21 g, 0.36 mmol) y monohidrato de hidrazina (0.69 mL) se agregaron junto con 8 mL de n-butanol. La mezcla se calentó a 120°C bajo N_2 durante 1 hora. El solvente se removió. El residuo se purificó por CLAR de fase inversa para dar 0.14 g del compuesto del título como la sal bis-TFA. EM: 492.3, $(M+H)^+$. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 0.82-0.84 (m, 2H), 1.11-1.22 (m, 2H), 1.36 (m, 1H), 1.52 (m, 1H), 1.61-1.70 (m, 3H), 2.02 (m, 1H), 2.52-2.61 (m, 2H), 2.94-3.09 (m, 2H), 5.15 (m, 1H), 7.13-7.20 (m, 5H), 7.77-8.27 (m, 3H).

Ejemplo 121

N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-4-(aminometil)benzamida, sal del ácido bistrifluoroacético

El Ejemplo 121 se preparó por la aplicación apropiada del procedimiento descrito por el Ejemplo 120, donde el ácido 4-((terc-butoxicarbamoil)metil)benzoico en lugar del ácido Boc-tranexámico se usa en el Ejemplo 120 Parte F. EM: 486.3, $(M+H)^+$. ^{1}HRMN (500 MHz, d_4-MeOH) δ 3.33-3.35 (m, 2H), 4.18 (s, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.22-7.25 (m, 5H), 7.52-7.55 (m, 3H), 7.72 (s, 1H) 7.88 (d, J = 8.25 Hz, 2H), 7.97 (d, J =

8.80 Hz, 1H).

Ejemplo 122

3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-1H-indazol-6-carboxamida, sal del ácido bis-trifluoroacético

Parte A: (S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletilcarbamato de terc-butilo: El producto de la Parte D del Ejemplo 120 (0.52 g, 1.2 mmol) se convirtió al aminoindazol por la aplicación apropiada del método descrito en la Parte H del Ejemplo 120. EM: 453.3 $(M+H)^+$.

Parte B: 6-(2-((S)-1-amino-2-feniletil)-5-cloro-1H-imidazol-4-il)-1H-indazol-3-amina: El grupo protegido por Boc en el producto del Ejemplo 122 Parte A se removió con TFA como se describe en la Parte G del Ejemplo 120. CL/EM: 353.1 $(M-H)^+$.

Parte C: N-((S)-1-(4-(3-Amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-4-ciano-3-fluorobenzamida: El producto del Ejemplo 122 Parte B se acopló con ácido 4-ciano-3-fluorobenzoico usando el método descrito en la Parte F del Ejemplo 120. EM: 500.3 $(M+H)^+$.

Parte D: 3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-

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5-cloro-1H-imidazol-2-il)-2-feniletil)-1H-indazol-6-carboxamida, sal del ácido bis-trifluoroacético: El producto del Ejemplo 122 Parte C se convirtió al Ejemplo 122 usando el método descrito en la Parte H del Ejemplo 120. EM: 510.3 $(M-H)^-$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.37 (m, 2H), 5.45 (t, J = 7.42 Hz, 1H), 7.23-7.27 (m, 5H), 7.54-7.58 (m, 2H), 7.72 (s, 1H), 7.86 (s, 1H), 7.91-7.97 (m, 2H).

Ejemplo 123

3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)benzo[d]isoxazol-6-carboxamida, sal del ácido bis-trifluoroacético

El producto de la Parte C del Ejemplo 122 se convirtió al aminobenzisoxazol con ácido acetohidroxámico y carbonato de potasio en DMF. EM: 513.1 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.37 (m, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.23-7.27 (m, 5H), 7.54 (d, J = 8.79 Hz, 1H), 7.68 (d, J = 8.24Hz, 1H), 7.72 (s, 1H), 7.82 (d, J = 8.24 Hz, 1H), 7.83 (s, 1H), 7.97 (d, J = 8.79 Hz, 1H).

Ejemplo 124

N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-4-(aminometil)-2-fluorobenzamida, sal del ácido bis-trifluoroacético

El Ejemplo 124 se preparó por la aplicación apropiada

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del procedimiento descrito por el Ejemplo 120, donde el ácido 4-ciano-2-fluorobenzoico en lugar del ácido Boc-tranexámico se usa en el Ejemplo 120 Parte F. El grupo ciano se redujo con $(Boc)_2O/NiCl_2/NaBH_4$ en MeOH a 0°C. El compuesto del título se aisló como la sal bis-TFA después de desprotección TFA por la aplicación apropiada del procedimiento descrito por el Ejemplo 2 Parte B. EM: 504.1, $(M+H)^+$. ^{1}H-RMN (400 MHz, d_4-MeOH) δ 3.34 (m, 2H), 4.18 (s, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.20-7.27 (m, 5H), 7.33-7.35 (m, 2H), 7.54 (dd, J = 8.34 Hz y 1.31 Hz, 1H), 7.75 (m,2H), 7.97 (d, J = 9.22 Hz, 1H).

Ejemplo 128

N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-4-cloro-2-fluorobenzamida, sal del ácido bis-trifluoroacético

El Ejemplo 128 se preparó similarmente por la aplicación apropiada del procedimiento por el Ejemplo 120, donde el ácido 4-cloro-2-fluorobenzoico en lugar de ácido Boc-tranexámico usado en el Ejemplo 120 Parte F. EM: 509.3, $(M+H)^+$. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 3.34 (m, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.21-7.34 (m, 7H), 7.53 (dd, J = 8.79 Hz y 1.1 Hz, 1H), 7.66 (t, J = 8.24 Hz, 1H), 7.72 (s, 1H), 7.99 (d, J = 8.79 Hz, 1H).

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Ejemplo 129

N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-2-fluoro-5-metoxibenzamida, sal del ácido bis-trifluoroacético

El Ejemplo 121 se preparó similarmente por la aplicación apropiada del procedimiento descrito por el Ejemplo 120, donde el ácido 2-fluoro-5-metoxibenzoico en lugar de ácido Boc-tranexámico se usó en el Ejemplo 120 Parte F. EM: 505.3, $(M+H)^+$. ^{1}H-RMN (500 MHz, d_4-MeOH) δ 3.34 (m, 2H), 3.78 (s, 3H), 5.44 (t, J= 7.42 Hz, 1H), 7.06 (m, 1H), 7.12 (m, 1H), 7.19 (m, 1H), 7.23-7.27 (m, 5H), 7.55 (dd, J = 8.79 Hz y 1.1 Hz, 1H), 7.73 (s, 1H), 7.98 (d, J = 8.79 Hz, 1H).

Ejemplo 130

(S)-4-[2-[(1-[4-(aminometil)ciclohexancarboxamido]-2-feniletil]-4-cloro-1H-imidazol-5-il]-benzamida, sal del ácido bis-trifluoroacético

El producto de la Parte A del Ejemplo 28 se cloró con NCS/$CHCl_3$ a temperatura ambiente usando el procedimiento descrito en el Ejemplo 120 Parte D. El grupo Boc luego se removió usando el procedimiento del Ejemplo 2 Parte B para dar el producto final como la sal bis-TFA. EM: 506.2 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.05 (m, 2H), 1.38 (m, 2H), 1.56 (m, 1H), 1.75 (m, 1H), 1.85 (d, J = 10.55 Hz, 3H), 2.20 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.17 (m, 2H), 5.20 (t, J =

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7.91 Hz, 1H), 7.21 (m, 5H), 7.73 (d, J = 8.79 Hz, 2H), 7.92 (d, J = 8.79 Hz, 2H).

Ejemplo 131

1-amida 4-({(S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-amida) del ácido trans-ciclohexan-1,4-dicarboxílico, sal del ácido bistrifluoroacético

El Ejemplo 131 se preparó similarmente por la aplicación apropiada del procedimiento por el Ejemplo 120, donde el ácido 4-trans-(metoxicarbonil)ciclohexanocarboxílico en lugar de ácido Boc-tranexámico se usa en el Ejemplo 120 Parte F. El éster de metilo intermediario luego se convirtió a la amida por aplicación secuencial del procedimiento usado por el Ejemplo 26 Parte A y Ejemplo 44 Parte A. EM: 506.2, $(M+H)^+$. ^{1}HRMN (500 MHz, d_4-MeOH) δ 1.33-1.38 (m, 1H), 1.45-1.48 (m, 3H), 1.72 (m, 1H) 1.88 (m, 3H), 2.18-2.23 (m, 2H), 3.17 (m, 1H), 3.26 (m, 1H), 5.21 (t, J = 7.42 Hz, 1H), 7.19 (m, 3H), 7.25 (m, 2H), 7.52 (dd, J=8.24 Hz y 1.1 Hz, 1H), 7.70 (s, 1H), 7.99 (d, J=8.24 Hz, 1H).

Ejemplo 132

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-1,4-bencendicarboxamida, sal del ácido bistrifluoroacético

El Ejemplo 132 se preparó por la aplicación apropiada

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del procedimiento descrito por el Ejemplo 120 en donde el ácido 4-carbamoilbenzoico se usa en lugar de ácido Boc-tranexámico en el Ejemplo 120 Parte F. EM: 500.1, $(M+H)^+$. ^{1}HRMN (500 MHz, d_4-MeOH) δ 3.34 (m, 2H), 5.44 (t, J = 7.42 Hz, 1H), 7.24-7.26 (m, 5H), 7.54 (dd, J = 8.79 y 1.1 Hz, 1H), 7.72 (s, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 8.79 Hz, 1H).

Ejemplo 135

(S)-4-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-feniletil]-4-fenil-1H-imidazol-5-il]-benzamida, sal del ácido bis-trifluoroacético

El producto de la Parte A del Ejemplo 28 se convirtió al éster de terc-butilo del ácido (4-{(S)-1-[5-bromo-4-(4-carbamoil-fenil)-1H-imidazol-2-il]-2-fenil-etilcarbamoil}-ciclohexilmetil)-carbámico por la aplicación apropiada del procedimiento del Ejemplo 82 Parte A. Este compuesto luego se acopló con ácido fenil borónico por la aplicación apropiada de las condiciones descritas por el Ejemplo 107 Parte B. La desprotección del grupo Boc con TFA usando el procedimiento del Ejemplo 2 Parte B proporciona el Ejemplo 135 como la sal bis-TFA. EM: 522.4 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.07 (m, 2H), 1.42 (m, 2H), 1.59 (m, 1H), 1.85 (m, 4H), 2.30 (m, 1H), 2.78 (d, J = 6.59 Hz, 2H), 3.41 (m, 2H), 5.32 (t, J = 8.13 Hz, 1H), 7.29 (m, 7H), 7.44 (m, 2H), 7.90 (d, J = 8.35 Hz, 2H).

Ejemplo 136

Sal del ácido bis-trifluoroacético de 1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-isoquinolin-6-carboxamida

Este producto se preparó usando ácido 1-aminoisoquinolin-6-carboxílico a partir de la Parte D del Ejemplo 147 y el producto a partir de la Parte E de Ejemplo 120 por aplicación secuencial de los procedimientos descritos por el Ejemplo 147 Parte F y el Ejemplo 120 Parte F. EM: 523.2 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.39 (dd, J = 15.82, 7.91 Hz, 2H), 5.48 (t, J = 7.91 Hz, 1H), 7.25-7.27 (m, 6H), 7.52 (d, J = 10.11 Hz, 1H), 7.61 (d, J = 7.03 Hz, 1H), 7.72 (s, 1H), 7.96 (d, J = 8.35 Hz, 1H), 8.08 (dd, J = 8.79, 1.76 Hz, 1H), 8.30 (s, 1H), 8.49 (d, J = 8.79 Hz, 1H).

Ejemplo 137

Sal del ácido bis-trifluoroacético de 1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-5,6,7,8-tetrahidroisoquinolin-6-carboxamida

El Ejemplo 137 se preparó a partir del producto de la Parte F del Ejemplo 147 por aplicación apropiada de los procedimientos del Ejemplo 120 Parte H. EM: 527.3 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 2.44 (m, 2H), 2.76 (m, 2H), 2.88 (m, 1H), 3.21 (m, 2H), 3.34 (m, 2H) 5.29 (m, 1H), 6.66 (t, J = 7.9 Hz, 1H), 7.24 (m, 5H), 7.56 (m, 2H), 7.73 (s, 1H), 7.97

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(d, J = 7.9 Hz, 1H).

Ejemplo 138

Sal del ácido bis-trifluoroacético de 2-(3-amino-1H-indazol-6-il)-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)acetamida

Este compuesto se preparó por la aplicación apropiada de los métodos descritos por el Ejemplo 122, en donde el ácido 2-(4-ciano-3-fluorofenil)acético se reemplazó por ácido 4-ciano-3-fluorobenzoico. EM: 526.3 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.17 (m, 1H), 3.26 (m, 1H), 3.69 (d, J = 5.71 Hz, 2H), 5.26 (t, J = 7.03 Hz, 1H), 7.02 (d, J= 8.34 Hz, 1H), 7.16 (m, 5H), 7.26 (s, 1H), 7.52 (d, J=8.79 Hz, 1H), 7.71 (s, 1H), 7.81 (d, J = 8.34 Hz, 1H), 7.97 (d, J = 8.79 Hz, 1H).

Ejemplo 139

Sal del ácido bis-trifluoroacético de trans-4-(2-{(S)-1-[(4-Aminometil-ciclohexancarbonil)-amino]-2-fenil-etil}-5-bromo-1-metil-1H-imidazol-4-il)-benzamida

El producto a partir del Ejemplo 82 Parte A se metiló con MeI/K_2CO_3/DMF. El isómero mayor aislado se desprotegió usando el procedimiento descrito por el Ejemplo 2 Parte B para dar el Ejemplo 139. EM: 538.2/540.2 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.04 (m, 2H), 1.39 (m, 2H), 1.56 (m,

1H), 1.80 (m, 4H), 2.20 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.27 (m, 2H), 3.41 (s, 3H), 5.35 (t, J = 7.91 Hz, 1H), 7.22 (m, 5H), 7.96 (m, 4H).

Ejemplo 140

Sal del ácido bis-trifluoroacético de 4-Aminometil-N-{(S)-1-[4-(4-carbamoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-2-etilamino-benzamida

Parte A: 4-Ciano-2-fluorobenzoato terc-butílico: El ácido 4-ciano-2-fluorobenzoico (1.0 g, 6.1 mmol) se disolvió en t-BuOH (9 mL) y THF (3 mL). El anhídrido Boc (2.64 g, 12.1 mmol) se agregó seguido por DMAP (0.24 g, 1.97 mmol). La mezcla se agitó a temperatura ambiente bajo N_2 durante 12 horas. Los solventes se removieron. El residuo se disolvió en EtOAc y se lavó con $NaHCO_3$ acuoso saturado y salmuera. Esto se secó sobre $MgSO_4$ y se concentró hasta un aceite el cual se volvió sólido bajo vació (1.3 g). ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.59 (s, 9H), 7.44 (dd, J = 25.71 y 9.01 Hz, 2H), 7.95 (m, 1H).

Parte B: 4-Ciano-2-(etilamino)benzoato terc-butílico: El producto a partir del Ejemplo 140 Parte A (0.30 g, 1.36 mmol) y clorohidrato de etilamina (0.22 g, 2.72 mmol) se agregaron junto con 5 mL de DMF. La mezcla se calentó a 50°C bajo N_2 durante 2 horas. Se agregó agua, y la mezcla se

extrajo con EtOAc. El extracto EtOAc se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró, y el residuo se purificó por cromatografía instantánea (sílice, EtOAc/hexano) para dar 50 mg del producto deseado. EM: 247.3 $(M+1)^+$.

Parte C: *Ácido 4-ciano-2-(etilamino)benzoico*: El producto a partir del Ejemplo 140 Parte B (50 mg, 0.20 mmol) se agitó con 5 mL de TFA y 5 mL de CH_2Cl_2 a temperatura ambiente durante 1 hora, y luego se calentó a reflujo durante 1 hora bajo N_2. El solvente se removió. El residuo se secó para dar 45 mg del ácido. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.28 (m, 3H), 3.18 (m, 2H), 76.75 (m, 1H), 6.86 (s, 1H), 7.95 (d, J = 7.91 Hz, 1H).

Parte D: *(S)-4-(2-(1-(1-(4-Ciano-2-(etilamino)fenil)vinilamino)-2-feniletil)-1H-imidazol-4-il)benzamida*: Ácido ciano-2-(etilamino)benzoico a partir del Ejemplo 140 Parte C (40 mg, 0.2 mmol), reactivo Bop (108 mg, 0.24 mmol), y Et_3N (0.28 mL) se agregaron junto con 5 mL de THF. La mezcla se agitó a temperatura ambiente durante 15 minutos y (S)-4-(2-(1-Amino-2-feniletil)-1H-imidazol-4-il)benzamida (107 mg, 0.2 mmol), se obtuvo a partir de N-boc-(L)-fenilalanina y se agregó 4-(2-Bromo-acetil)-benzonitrilo por la aplicación secuencial de los procedimientos descritos por el Ejemplo 1 Parte A, Ejemplo 28 Parte A y Ejemplo 1 Parte B. La mezcla resultante se calentó a reflujo bajo N_2

durante 2 horas. Los solventes se removieron. El residuo se disolvió en EtOAc y se lavó con agua y salmuera. Esto se secó sobre $MgSO_4$, se concentró, y purificó por cromatografía instantánea ISCO (sílice, EtOAc/hexano) para dar 50 mg del producto deseado. CL/EM: 479.3 $(M+1)^+$.

Parte E: Sal del ácido bis-trifluoroacético de 4-Aminometil-N-{(S)-1-[4-(4-carbamoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-2-etilamino-benzamida: El producto a partir del Ejemplo 140 Parte D se disolvió en 10 mL de MeOH y 1 mL de HCl 4N en dioxano. Una cantidad catalítica de Pd/C (10%) se agregó. La mezcla se colocó bajo un globo de H_2 durante 12 horas. Esto se filtró a través de Celite, se concentró, y purificó por CLAR de fase inversa para dar 24 mg de sal bis-TFA. CL/EM: 483.4 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.22 (t, J = 7.25 Hz, 3H), 3.18 (q, J = 7.03 Hz, 2H), 3.47 (dd, J = 32.52 y 8.35 Hz, 2H), 4.05 (s, 2H), 5.50 (t, J = 8.35 Hz, 1H), 6.66 (d, J = 7.91 Hz, 1H), 6.77 (s, 1H), 7.26 (m, 5H), 7.70 (d, J = 7.91 Hz, 1H), 7.76 (d, J = 8.35 Hz, 2H), 7.88 (s, 1H), 7.98 (d, J = 8.35 Hz, 2H).

Ejemplo 142

(S)-N-(1-(4-(4-Carbamoilfenil)-1H-imidazol-2-il)-2-feniletil)-1,2,3,4-tetrahidroisoquinolin-6-carboxamida

El Ejemplo 142 se preparó por aplicación apropiada

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de los métodos descritos en el Ejemplo 28. EM: 466.2 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.15 (t, J = 6.37 Hz, 2H), 3.49 (m, 4H), 4.41 (s, 2H), 5.53 (t, J = 8.35 Hz, 1H), 7.27 (m, 6H), 7.75 (m, 4H), 7.88 (s, 1H), 7.97 (d, J = 8.79 Hz, 2H).

Ejemplo 143

4-Aminometil-N-{(S)-1-[4-(4-carbamoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-2-etil-benzamida

Parte A: 4-Bromo-2-clorobenzoato de metilo: El ácido 2-bromo-4-clorobenzoico (1.0 g, 4.25 mmol) se disolvió en 10 mL de MeOH. La mezcla se enfrió en un baño de hielo y a esto se le agregó cloruro de tionilo (3.1 mL, 42.5 mmol) gota a gota. El baño de enfriamiento se removió y la mezcla se agitó a temperatura ambiente bajo N_2 durante 12 horas. El solvente se removió y se secó bajo vació para dar 1.0 g de aceite incoloro. CL/EM: 251.1 $(M+1)^+$.

Parte B. 2-Cloro-4-cianobenzoato de metilo: El producto a partir del Ejemplo 143 Parte A (1.0 g, 4.0 mmol), $Zn(CN)_2$ (0.52 g, 4.8 mmol), $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol) se agregaron junto con 9 mL de DMF. La mezcla se desgasificó y luego se calentó a 90°C durante 6 horas. El agua y EtOAc se agregaron a la mezcla de reacción. Esto se filtró para remover los sólidos inorgánicos. Las capas se separaron y la capa de EtOAc se lavó con agua y salmuera. Esto se secó sobre

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$MgSO_4$, se concentró, y purificó por cromatografía instantánea (sílice, EtOAc/hexano) para dar 0.28 g del producto deseado. EM: 196.1 $(M+1)^+$.

Parte C: 4-Ciano-2-etilbenzoato de metilo: El producto del Ejemplo 143 Parte B (160 mg, 0.82 mmol), ácido etil borónico (120 mg, 1.64 mmol), K_3PO_4 344 mg (1.64 mmol), y $Pd(PPh_3)_4$ (114 mg, 0.1 mmol) se agregaron junto con 9 mL de DME. La mezcla se calentó a 150°C en microondas durante 15 minutos. El DME se removió y EtOAc se agregó. Esto se lavó con agua y salmuera, se secó sobre $MgSO_4$, se concentró y se purificó por cromatografía instantánea (sílice, EtOAc/hexano) para dar 100 mg del producto deseado. EM: 190.21 $(M+H^+)^+$ y 222.3 $(M+Na^+)^+$.

Parte D: Ácido 4-ciano-2-etilbenzoico: El producto del Ejemplo 143 Parte C (100 mg, 0.53 mmol) se disolvió en 5 mL de EtOH y 1 mL de NaOH acuoso 1N se agregó. La mezcla se agitó a temperatura ambiente bajo N_2 durante 2 horas. El HCl acuoso 1N se agregó hasta ajustar el pH hasta 4. El EtOH se removió, y la mezcla se diluyó con EtOAC y agua. Las dos capas se separaron. La capa de agua se extrajo con EtOAc. La solución EtOAc combinada se lavó con agua y salmuera, se secó sobre $MgSO_4$, y se concentró para dar 90 mg del ácido deseado. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.22 (m, 3H), 3.00 (m, 2H), 7.71

(m, 1H), 7.67 (s, 1H), 7.92 (d, J = 8.35 Hz, 1H).

Parte E: N-{(S)-1-[4-(4-carbamoil-fenil)-1H-imidazol-2-il)-2-fenil-etil}-4-ciano-2-etil-benzamida: El producto a partir del Ejemplo 143 Parte D (90 mg, 0.51 mmol), reactivo Bop (265 mg, 0.61 mmol), y trietilamina (0.42 mL, 1.5 mmol) se agregaron junto con 5 mL de THF. La mezcla se agitó a temperatura ambiente bajo N_2 durante 15 minutos y la (S)-4-(2-(1-amino-2-feniletil)-1H-imidazol-4-il)benzamida se preparó usando los métodos descritos en los Ejemplos 2 y 28 (365 mg, 0.51 mg) se agregó. La mezcla resultante se calentó a 75°C durante 70 minutos. El THF se removió, y el residuo se disolvió en EtOAc. Esto se lavó con agua y salmuera, se secó sobre $MgSO_4$, se concentró, y se purificó por cromatografía instantánea (sílice, EtOAc/hexano) para dar 80 mg del producto deseado. EM: 464.4 $(M+1)^+$.

Parte F: 4-Aminometil-N-{(S)-1-[4-(4-carbamoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-2-etil-benzamida: El producto a partir del Ejemplo 143 Parte E (70 mg, 0.15 mmol) se disolvió en 10 mL de MeOH y 1 mL de HCl 4 N en dioxano. Una cantidad catalítica de Pd/C (10%) se agregó y la mezcla se colocó bajo un globo de H_2 durante 6 horas. Esto se filtró a través de Celite y se lavó con MeOH. El filtrado se concentró y purificó por CLAR de fase inversa para dar 75 mg

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de la sal bis-TFA. CL/EM: 468.4 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.08 (t, J = 7.47 Hz, 3H), 2.61 (t, J = 7.47 Hz, 2H,), 3.44 (dd, J = 13.62, 8.35 Hz, 2H), 4.12 (s, 2H), 5.59 (t, J = 8.35 Hz, 1H), 7.34 (m, 7H), 7.80 (d, J = 8.35 Hz, 2H), 7.89 (s, 1H), 7.99 (d, J = 8.35 Hz, 2H).

Ejemplo 144

Sal del ácido bis-trifluoroacético de 3-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-1-metil-1H-indazol-6-carboxamida

El producto a partir de la Parte C del Ejemplo 122 se convirtió al producto deseado por aplicación apropiada del método descrito en la Parte H del Ejemplo 120, donde la hidrazina de metilo se usó en lugar de hidrazina. EM: 526.3 $(M+H)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 3.35 (m, 2H), 3.84 (s, 3H), 5.46 (m, 1H), 7.23 (m, 5H), 7.39 (d, J = 8.35 Hz, 2H), 7.64 (s, 1H), 7.72 (d, J = 8.35 Hz, 1H), 7.79 (s, 1H), 7.84 (d, J = 7.91 Hz, 1H).

Ejemplo 147

Sal del ácido bis-trifluoroacético de 1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-5,6,7,8-tetrahidroisoquinolin-6-carboxamida

Parte A: (E)-2-(2-(Dimetilamino)vinil)tereftalonitrilo: El

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metiltereftalonitrilo (1.42 g, 1.0 mmol) y t-butoxibis(dimetilamina)metano (3.5 g, 2.0 mmol) se calentaron con 15 mL de DML a 75°C durante 12 horas bajo N_2. El DMF se removió y el hexano se agregó. El precipitado formado se filtró y se secó para dar 1.85 g del producto deseado. EM: 504.4, $(M+H)^+$. ^{1}H-RMN (400 MHz, d_4-MeOH) δ 2.95 (s, 6H), 5.27 (d, J = 13.62 Hz, 1H), 7.14 (m, 1H), 7.42 (d, J = 13.18 Hz, 1H), 7.54 (d, J = 7.91 Hz, 1H), 7.86 (s, 1H).

Parte B: 2-(2,4-Dimetoxibencil)-1-imino-1,2-dihidroisoquinolin-6-carbonitrilo: El producto del Ejemplo 147 Parte A (1.85 g, 9.38 mmol) y 2,4-dimetoxibencilamina (2.6 mL, 15.03 mmol) se calentaron con 5 mL de DMPU a 140°C durante 3 horas bajo N_2. La mezcla de reacción se enfrió, y el EtOAc/hexano (1:2) se agregó. El precipitado formado se filtró y se secó in vacuo para dar 2.5 g del producto deseado. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 3.72 (s, 3H, 3.81 (s, 3H), 4.95 (s, 2H), 6.10 (d, J = 7.03 Hz, 1H, 6.44 (d, J = 7.91 Hz, 1H), 6.57 (s, 1H), 7.02 (d, J = 8.35 Hz, 1H), 7.22 (d, J = 6.15 Hz, 1H,) 7.68 (d, J = 7.91 Hz, 1H), 7.94 (s, 1H), 8.34 (d, J = 7.91 Hz, 1H).

Parte C: 2-(2,4-Dimetoxibencil)-1-imino-1,2-dihidroisoquinolin-6-carboxílico: El producto del Ejemplo 147 Parte B (2.5 g, 7.84 mmol) se calentó con 40 mL del MeOH-NaOH

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15% (1:1) a 90°C durante 1.5 hora bajo N_2. La mezcla de reacción se enfrió y el HCl acuoso se agregó gota a gota para ajustar el pH hasta alrededor de 5. El metanol se removió y el EtOAc/hexano (1:2) se agregó. El precipitado formado se filtró y se secó para dar 2.42 g del producto deseado. CL/EM: 339.2, $(M+H)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 2.00 (s, 2H), 3.82 (d, J = 9.67 Hz, 6H), 6.62 (m, 2H), 7.23 (d, J = 7.91 Hz, 2H), 7.50 (d, J = 7.03 Hz, 1H), 8.23 (s, 1H), 8.31 (s, 1H), 8.42 (d, J = 8.79 Hz, 1H).

Parte D: Ácido 1-Aminoisoquinolin-6-carboxílico: El producto del Ejemplo 147 Parte C (2.12 g, 6.28 mmol) se calentó con 17 mL de anisol y 20 mL de TFA a 105°C durante 12 horas bajo N_2. Los solventes se removieron, y EtOAc/hexano (1:2) se agregaron. El precipitado formado se filtró y se secó para dar 1.77 g de la sal TFA. CL/EM: 189.04, $(M+H)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 7.34 (d, J = 7.03 Hz, 1H), 7.62 (d, J = 7.03 Hz, 1H), 8.30 (d, J = 8.79 Hz, 1H), 8.51 (d, J = 8.79 Hz, 1H), 8.56 (s, 1H).

Parte E: Ácido 1-Amino-5,6,7,8-tetrahidroisoquinolin-6-carboxílico: El producto del Ejemplo 147 Parte D (1.0 g, 3.31 mmol) y óxido de platino (87 mg, 0.38 mmol) se agregaron junto con 21 mL de TFA. La mezcla de reacción se colocó bajo un globo de gas de hidrógeno y luego

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se entibió a 60°C durante 16 horas. La mezcla se enfrió a temperatura ambiente y se filtró a través de Celite para remover el óxido de platino. El solvente se removió, y el residuo se purificó por CLAR de fase inversa para dar 0.21 g del producto deseado como la sal TFA. CL/EM: 193.1, $(M+H)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 2.00 (m, 1H), 2.28 (m, 1H), 2.57 (m, 2H,) 2.85 (m, 1H), 3.02 (d, J = 7.03 Hz, 2H), 6.75 (d, J = 6.59 Hz, 1H), 7.61 (d, J = 6.59 Hz, 1H).

Parte F: 1-Amino-N-((S)-1-(4-cloro-5-(4-ciano-3-fluorofenil)-1H-imidazol-2-il)-2-feniletil)-5,6,7,8-tetrahidroisoquinolin-6-carboxamida: El producto del Ejemplo 147 Parte E (0.21 g, 0.67 mmol), reactivo Bop (0.44 g, 1.0 mmol), y trietilamina (0.91 mL, 6.54 mmol) se agregaron junto con 15 mL de THF. La mezcla se agitó a temperatura ambiente durante 20 minutos bajo N_2 y el producto de la Parte E del Ejemplo 120 (0.41 g, 0.90 mmol) se agregó. La mezcla resultante se calentó a 75°C durante 1 hora bajo N_2. La mezcla de reacción se enfrió y el solvente se removió. El residuo se disolvió en EtOAc y se lavó con agua y salmuera. Esto se secó sobre $MgSO_4$, se concentró, y purificó por cromatografía instantánea (40 g sílice, 0-15% MeOH en diclorometano) para dar 0.31 g del producto deseado. CL/EM: 515.4, $(M+H)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.73 (dd, J = 12.96, 5.93 Hz, 1H), 2.10 (m, 1H) 2.39 (m, 1H), 2.58 (m, 4H), 3.22

(m, 2H), 5.24 (t, J = 7.69 Hz, 1H), 6.37 (d, J = 5.27 Hz, 1H), 7.23 (m, 5H), 7.64 (m, 3H,) 7.79(m, 1H).

Parte G: Separación Quiral del producto de la Parte F: El producto del Ejemplo 147 Parte F se separó por CLAR preparativa quiral (columna OD, 30% EtOH/MeOH (1:1) y heptano al 70% con 0.15% DEA) para dar el diaestereómero A y diaestereómero B.

Parte H: ((S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil]-amida del ácido (S)-1-Amino-5,6,7,8-tetrahidro-isoquinolin-6-carboxílico: El diaestereómero A del Ejemplo 147 Parte G (0.10 g, 0.19 mmol) e hidrazina (0.50 mL) se agregaron junto con 7 mL de n-butanol. La mezcla se calentó a 120°C bajo N_2 durante 1.5 hora. El solvente se removió. El residuo se purificó por CLAR de fase inversa para dar 0.10 g del producto deseado como la sal bis-TFA. CL/EM: 527.21, $(M+H)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.84 (m, 1H), 2.14 (m, 1H), 2.51 (m, 2H), 2.72 (m, 3H), 3.19 (m, 2H), 5.24 (m, 1H), 6.66 (d, J = 6.59 Hz, 1H), 7.24 (m, 5H), 7.49 (d, J = 8.35 Hz, 1H), 7.59 (d, J = 6.59 Hz, 1H) 7.69 (s, 1H), 7.93 (d, J = 9.23 Hz, 1H).

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Ejemplo 155

Sal del ácido bis-trifluoroacético de N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-1,2,3,4-tetrahidroisoquinolin-6-carboxamida

El Ejemplo 155 se preparó por aplicación apropiada de los procedimientos descritos por el Ejemplo 120, donde el ácido 2-(tert-butoxicarbonil)-1,2,3,4-tetrahidroisoquinolin-6-carboxílico en lugar del ácido Boc-tranexámico se usó en el Ejemplo 120 Parte F. EM: 512.2, $(M+H)^+$. ^{1}H-RMN (400 MHz, d_4-MeOH) δ 3.17 (t, J = 6.37 Hz, 2H, 3.35 (m, 2H) 3.53 (t, J = 6.37 Hz, 2H), 4.41 (s, 2H), 5.41 (t, J = 7.91 Hz, 1H), 7.22 (m, 5H), 7.32 (d, J = 8.35 Hz, 1H), 7.50 (d, J = 10.11 Hz, 1H) 7.71 (m, 3H) 7.94 (d, J = 8.35 Hz, 1H).

Ejemplo 157

Sal del ácido tris-trifluoroacético de {(S)-1-[5-(3-Amino-1H-indazol-6-il)-1H-imidazol-2-il]-3-[(piridin-2-ilmetil)-carbamoil]-propil}-amida del ácido trans-4-aminometil-ciclohexanocarboxílico,

Parte A: Éster de 1-[2-(4-ciano-3-fluoro-fenil)-2-oxo-etilo] del éster de 5-tert-butilo del ácido (S)-2-benciloxicarbonilamino-pentanodioico: El éster de 5-tert-butilo del ácido (S)-2-benciloxicarbonilamino-pentanodioico (674 mg, 2 mmol), Cs_2CO_3 (326 mg, 1 mmol) y DMF 5 mL) se agitaron a temperatura ambiente durante 0.5 hora. Una

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solución de 1'-bromo-3-fluoro-4-cianoacetofenona (484 mg, 2 mmol) en DMF (5 mL) se agregó. Se continuó agitando durante 16 horas. La mezcla de reacción se diluyó con EtOAc (100 mL). Tres lavados con una solución LiCl 10%, secando sobre $MgSO_4$, la filtración y remoción del solvente in vacuo proporcionó un aceite anaranjado (900 mg, 91% de rendimiento): ^{1}H-RMN ($CDCl_3$, 400 MHz): δ 7.77 (m, 3H), 7.35 (m, 5H), 5.52 (m, 1H), 5.42 (d, 1H, J = 16), 5.25 (d, 1H, J = 16), 5.11 (s, 2H), 4.60 (m, 1H), 2.45 (m, 2H), 1.44 (s, 9H); EM: 497 (M-H+)-.

Parte B: Éster terc-butílico del ácido (S)-4-benciloxicarbonilamino-4-[5-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il)-butírico: El intermediario del Ejemplo 157 Parte A (900 mg, 1.81 mmol), NH_4OAc (1.54 g, 20 mmol) y xilenos (30 mL) se agitaron a temperatura de reflujo durante 2.5 horas. La mezcla de reacción se enfrió a temperatura ambiente. El solvente se removió in vacuo. El residuo se dividió entre EtOAc y una solución Na_2CO_3 saturada tres veces. Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se filtraron. El solvente se removió in vacuo para dar un aceite anaranjado rojizo. La CLAR (0% hasta 100% EtOAc-hexanos) dio un aceite color anaranjado (400 mg, 46% de rendimiento): ^{1}H-RMN ($CDCl_3$, 400 MHz): δ 10.3 (s, 1H), 7.59 (m, 4H), 7.35 (m, 5H), 5.83 (s, 1H), 5.13 (m, 2H), 4.79 (m, 1H), 2.53 (m, 1H), 2.34 (m, 3H), 1.45 (s, 9H); EM: 477 (M-H+)-.

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Parte C: Éster terc-butílico del ácido (S)-4-Amino-4-[5-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-butírico: El intermediario a partir del Ejemplo 157 Parte B (400 mg, 0.84 mmol), Pd en C al 10% (40 mg) y EtOH (4 mL) se agitaron bajo una atmósfera de hidrógeno durante 2 horas. La mezcla de reacción se filtró a través de Celite. El solvente se removió in vacuo para dar un aceite. La CLAR (0% hasta 10% MeOH-CH_2Cl_2) proporcionó un sólido amarillo pálido (189 mg, 65% de rendimiento): ^{1}H-RMN ($CDCl_3$, 400 MHz): δ 10.3 (s, 1H), 7.59 (m, 2H), 7.34 (1, 2H), 4.81 (t, 1H, J = 7), 2.59 (m, 2H), 2.28 (m, 2H), 1.42 (s, 9H); EM: 343 ($M-H^+$)-.

Parte D: Éster terc-butílico del ácido trans-(S)-4-{[4-(benciloxicarbonilamino-metil)-ciclohexanocarbonil]-amino)-4-[5-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-butírico: El ácido N-CBz-tranexámico (160 mg, 0.66 mmol), HOBt·H_2O (82 mg, 0.61 mmol), EDCI (117 mg, 0.61 mmol), $(i\text{-}Pr)_2NEt$ (388 mg, 0.52 mL, 3 mmol) y DMF (1 mL) se agitaron a temperatura ambiente durante 15 minutos. Una solución del intermediario a partir del Ejemplo 157 Parte C (189 mg, 0.55 mmol) en DMF (1 mL) se agregó. Se continuó agitando durante 24 horas. La mezcla de reacción se diluyó con EtOAc (40 mL). La mezcla orgánica se lavó con una solución LiCl al 10%. Secando sobre $MgSO_4$, la filtración y remoción del solvente in vacuo proporcionó un sólido color marrón (330 mg, 97% de

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rendimiento): ^{1}H-RMN ($CDCl_3$, 400 MHz): δ 10.1 (s, 1H), 7.60 (m, 1H), 7.35 (m, 2H), 6.97 (d, 1H, J = 8), 5.09 (s, 2H), 4.90 (d, 1H, J = 8), 4.81 (m, 1H), 3.06 (t, 2H, J = 7), 2.37 (m, 2H), 2.27 (m, 1H), 1.87 (m, 2H), 1.46 (s, 9H), 1.03 (m, 2H); EMAR (ES^+): Calculado para $C_{34}H_{41}FN_5O_5$: 618.3092, Encontrado: 618.3098 $(M+H+)^+$.

Parte E: Ácido trans-(S)-4-[[4-(benciloxicarbonilamino-metil)-ciclohexanocarbonil]-amino)-4-[5-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-butírico: El intermediario a partir del Ejemplo 157 Parte D (330 mg, 0.53 mmol), TFA (0.5 mL) y CH_2Cl_2 (0.5 mL) se agitaron a temperatura ambiente durante 2 horas. El solvente se removió in vacuo para dar un sólido color marrón (300 mg, 100% de rendimiento): ^{1}H-RMN (DMSO-d_6, 400 MHz): δ 8.24 (m, 1H), 8.04 (s, 1H), 7.97 (m, 1H), 7.88 (d, 1H, J = 9), 7.81 (d, 1H, J = 9), 7.35 (m, 6H), 7.25 (m, 1H), 5.01 (s, 2H), 5.0 (m, 1H), 3.63 (m, 1H), 3.13 (m, 1H), 2.86 (m, 2H), 2.31 (m, 2H), 2.15 (m, 2H), 2.04 (m 1H), 1.75 (m, 2H), 1.27 (m, 5H), 0.88 (m, 1H); EMAR (ES^+): Calculado para $C_{30}H_{33}FN_5O_5$: 562.2466, Encontrado: 562.2453 $(M+H)^+$.

Parte F: Éster bencílico del ácido trans-(4-[(S)-1-[5-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-3-[(piridin-2-ilmetil)-carbamoil]-propilcarbamoil)-ciclohexilmetil)-carbámico: El intermediario a partir del Ejemplo 157 Parte E

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(325 mg, 0.53 mmol), HOBt·H_2O (81 mg, 0.6 mmol), EDC (115 mg, 0.6 mmol), $(i\text{-}Pr)_2NEt$ (388 mg, 0.52 mL, 3.0 mmol) y DMF (1 mL) se agitaron a temperatura ambiente bajo una atmósfera de nitrógeno durante 15 minutos. La 2-aminometilpiridina (65 mg, 0.6 mmol) se agregó, y se continuó agitando durante 88 horas. La mezcla de reacción se diluyó con EtOAc (20 mL) y la mezcla orgánica se lavó con una solución de LiCl al 10% (5 mL) tres veces. La capa orgánica se secó sobre $MgSO_4$ y se filtró. El solvente se removió in vacuo. La CLAR (0% hasta 10% MeOH-CH_2Cl_3) proporcionó un sólido amarillo pálido (40 mg, 12% de rendimiento): ^{1}H-RMN (MeOH-d_4, 400 MHz): δ 8.49 (m, 1H), 7.81 (t, 1H, J = 8), 7.73 (m, 2H), 7.35 (m, 11H), 5.08 (s, 1H), 4.50 (s, 2H), 3.37 (m, 4H), 2.98 (d, 2H, J = 7), 2.40 (m, 2H), 2.25 (m, 2H), 1.86 (m, 6H), 1.47 (m, 2H), 1.05 (m, 2H); EMAR (ES^+): Calculado para $C_{36}H_{39}FN_7O_4$: 652.3048, Encontrado: 652.3063 (M+H).

Parte G: Sal del ácido tris-trifluoroacético de {(S)-1-[5-(4-Ciano-3-fluoro-fenil)-1H-imidazol-2-il]-3-[(piridin-2-ilmetil)-carbamoil]-propil}-amida del ácido trans-4-aminometil-ciclohexanocarboxílico: El intermediario del Ejemplo 157 Parte F (98 mg, 0.15 mmol) y una solución de HBr en ácido acético (33%, 3 mL) se agitaron a temperatura ambiente durante 21 horas. El solvente se removió in vacuo para proporcionar un aceite. La CLAR de fase inversa (0%

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hasta 100% CH_3CN-H_2O con 0.1% TFA) proporcionó un sólido blanco (20 mg, 39% de rendimiento): ^{1}H-RMN (MeOH-d_4, 400 MHz): δ 8.70 (d, 1H, J = 5), 8.38 (t, 1H, J = 8), 8.00 (s, 1H), 7.80 (m, 5H), 5.18 (t, 1H, J = 6), 4.93 (m, 5H), 4.69 (d, 1H, J = 16), 4.63 (d, 1H, J = 16), 2.78 (d, 2H, J = 7), 2.51 (m, 2H), 2.31 (m, 4H), 1.62 (m, 2H), 1.45 (m, 4H), 1.09 (m, 2H); EMAR (ES^+): Calculado para $C_{28}H_{33}FN_7O_2$: 518.2680, Encontrado: 518.2698 (M+H).

Parte H: Sal del ácido tris-trifluoroacético de [(S)-1-[5-(3-Amino-1H-indazol-6-il)-1H-imidazol-2-il]-3-[(piridin-2-ilmetil)-carbamoil]-propil}-amida del ácido trans-4-aminometil-ciclohexanocarboxílico: El intermediario del Ejemplo 157 Parte F (20 mg, 0.02 mmol), hidrato de hidrazina (0.5 mL) y n-BuOH (0.5 mL) se calentaron en un aparato de microondas durante 15 minutos a 120°C. El solvente se removió in vacuo para proporcionar un sólido blanco (10 mg, 49% de rendimiento): ^{1}H-RMN (MeOH-d_4, 400 MHz): δ 8.48 (d, 1H, J = 2), 7.80 (t, 1H, J = 8), 7.67 (m, 2H), 7.35 (m, 4H), 5.11 (t, 1H, J = 7), 4.86 (m, 8H), 4.50 (s, 2H), 3.57 (t, 1H, J = 7), 2.81 (d, 2H, J = 7), 2.39 (m, 2H), 2.24 (m, 4H), 1.95 (m, 4H), 1.53 (m, 2H), 0.96 (t, 2H, J = 7); EMAR (ES^+): Calculado para $C_{28}H_{36}N_9O_2$: 530.2992, Encontrado: 530.2991 (M + H)

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Ejemp1 158

{(S)-1-[5-Fenil-1H-imidazol-2-il]-3-[(piridin-2-ilmetil)-carbamoil]-etil}-amida del ácido trans-4-aminometil-ciclohexancarboxílico

Este compuesto se preparó siguiendo los procedimientos descritos en el Ejemplo 157, Partes A hasta H: ^{1}H-RMN (MeOH-d_4, 400 MHz): δ 8.30 (d, 1H, J = 8), 7.58 (d, 2H, J = 8), 7.43 (t, 1H, J = 8), 7.25 (m, 3H), 7.13 (m, 2H), 7.05 (d, 1H, J = 8), 5.40 (t, 1H, J = 7), 4.76 (m, 5H), 4.38 (d, 1H, J = 16), 4.30 (d, 1H, J = 16), 2.94 (dd, 1H, J = 15, 7), 2.84 (dd, 1H, J = 15,7), 2.43 (d, 2H, J = 7), 2.10 (m, 1H), 1.77 (m, 4H), 1.34 (m, 4H), 0.89 (m, 1H); EMAR (ES$^+$): Calculado para $C_{26}H_{33}N_6O_2$: 461.2665, Encontrado: 461.2657 (M + H).

Ejemplo 159

Sal del ácido bis-trifluoroacético de N-[2-(2S)-[2-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[[trans-[4-(aminometil)ciclohexanocarboxamido]etil]fenil]-fenilacetamida

Parte A: Éster terc-butílico del ácido trans-{4-[(S)-1-[4-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-2-(2-nitro-fenil)-etilcarbamoil]-ciclohexilmetil}-carbámico: La L-2-Nitro-N-(Boc)-fenilalanina (2.24 g, 7.23 mmol) se trató secuencialmente de conformidad con los procedimientos descritos en el Ejemplo 1 parte A y Parte B y el Ejemplo 2

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parte A para producir 3.0 g (98% de rendimiento) del producto deseado. EM 450 $(M-H)^-$.

Parte B: Éster terc-butílico del ácido trans-(4-{(S)-2-(2-Amino-fenil)-1-[4-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-etilcarbamoil}-ciclohexilmetil)-carbámico: El producto del Ejemplo 159 Parte A (284 mg, 0.48 mmol) se disolvió en ácido acético (3.5 mL) y 5 gotas de agua. El polvo de hierro (273 mg, 4.8 mmol) se agregó al matraz, y la reacción se calentó hasta 50°C durante 5 horas. La reacción se enfrió a temperatura ambiente, se diluyó con 50 mL de MeOH, y se filtró a través de Celite. Los solventes se removieron in vacuo para producir 265 mg (98% de rendimiento) de la anilina cruda. EM 559 (M-H)-.

Parte C: Éster terc-butílico del ácido trans-{4-[(S)-1-[4-(4-ciano-3-fluoro-fenil)-1H-imidazol-2-il]-2-(2-fenilacetilamino-fenil)-etilcarbamoil]-ciclohexilmetil}-carbámico: El producto del Ejemplo 159 Parte B (132 mg, 0.23 mmol) y ácido fenil acético (40 mg, 0.28 mmol) se disolvieron en piridina (0.7 mL, 0.71 mmol) y 1.5 mL de DMF. El HOBt (45 mg, 0.3 mmol) y EDCI (60 mg, 0.30 mmol) se agregaron al matraz, y la reacción se agitó a temperatura ambiente durante 12 horas. La reacción se diluyó con EtOAc, se extrajo con salmuera 1/2 saturada (4-6 veces), se secó sobre $MgSO_4$, se

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filtró y evaporó hasta secarse para producir el producto deseado 150 mg (95% de rendimiento). EM 677 (M-H)-.

Parte E: [(S)-1-[4-(4-Ciano-3-fluoro-fenil)-1H-imidazol-2-il]-2-(2-fenilacetilamino-fenil)-etil]-amida del ácido trans-4-Aminometil-ciclohexanocarboxílico: El producto del Ejemplo 159 parte C (150 mg, 0.22 mmol) se trató bajo la condición descrita en el Ejemplo 2 parte B y se purificó por CLAR preparativa (MeOH/H_2O/0.1% gradiente TFA) para producir 18 mg (14% de rendimiento) del producto deseado. EM 577 (M-H)-.

Parte F: Sal del ácido bis trifluoroacético de [(S)-1-[4-(3-Amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(2-fenilacetilamino-fenil)-etil]-amida del ácido trans-4-aminometil-ciclohexanocarboxílico: El producto del Ejemplo 159 Parte D (18 mg, 0.03 mol) se trató bajo las condiciones descritas en el Ejemplo 120 Parte H hasta producir 2.3 mg (11% de rendimiento) del Ejemplo 159. ^{1}H RMN (500 MHz, MeOH-d_4) δ 0.93-1.11 (m, 1H) 1.35 (ddd, J=58.97, 12.78, 3.57 Hz, 1H) 1.48-1.62 (m, 1H) 1.59-1.73 (m, 1H) 1.74-1.92 (m, 2H) 2.10-2.31 (m, 1H) 2.76 (d, J=7.15 Hz, 1H) 3.75 (q, J=13.75 Hz, 1H) 5.24 (t, J=8.25 Hz, 1H) 7.05-7.22 (m, 2H) 7.26-7.33 (m, 1H) 7.37 (t, J=6.60 Hz, 2H) 7.63 (s, 1H) 7.78 (s, 1H) 7.88 (d, J=8.80 Hz, 1H) EMAR m/z Calculado para $C_{34}H_{39}N_8O_2$ (M +

H)$^+$: 591.3196 Encontrado 591.3221.

Ejemplo 162

Sal del ácido bis-trifluoroacético de (S)-4-(aminometil)-N-[1-[4-(4-amino-7-quinazolinil)-5-cloro-1H-imidazol-2-il]-2-feniletil]-trans-ciclohexanocarboxamida

Parte A: Éster terc-butílico del ácido (4-{(S)-1-[4-(4-amino-quinazolin-7-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etilcarbamoil)-ciclohexilmetil)-carbámico: El producto del Ejemplo 120 Parte F (0.53 g, 0.9 mmol) y acetato de formamidina (1.5 g, 14.4 mmol) se agregaron junto con 20 mL de DMAC. La mezcla se calentó a 140°C bajo N_2 durante 8 horas. Formamidina adicional (1.5 g, 14.4 mmol) se agregó, y la mezcla se calentó durante 12 horas adicionales. La mezcla se enfrió y se agregó agua. La mezcla se ajustó a un pH 7 con $NaHCO_3$ acuoso, y se extrajo luego con EtOAc. Los extractos de EtOAC combinados se lavaron con salmuera, se secaron sobre $MgSO_4$, se concentraron, y se purificaron por cromatografía instantánea (120 g sílice, 0-10% MeOH en CH_2Cl_2) para dar 80 mg del producto deseado. CL/EM: 604.1, 606.1, $(M+H)^+$.

Parte B: Sal del ácido bis-trifluoroacético de {(S)-1-[4-(4-Amino-quinazolin-7-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-amida del ácido 4-aminometil-ciclohexanocarboxílico: El producto del Ejemplo 162 Parte A

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(80 mg, 0.13 mmol) se agitó con CH_2Cl_2 (5 mL) y TFA (2 mL) bajo N_2 durante 0.5 horas. Los solventes se removieron. El residuo se purificó por CLAR de fase inversa para dar 75 mg del producto deseado como la sal bis-TFA. EM: 504.4, $(M+H)^+$. ^{1}H-RMN (400 MHz, d_4-MeOH) δ 1.02-1.06 (m, 2H), 1.34-1.47 (m, 2H), 1.55 (bs, 1H), 1.75-1.90 (m, 4H), 2.22 (m, 1H), 2.76 (d, J = 7.03 Hz, 2H), 3.12-3.24 (m, 2H), 5.20 (m, 1H), 7.16-7.22 (m, 5H), 8.00 (m, 1H), 8.13 (s, 1H), 8.34 (m, 1H), 8.65 (s, 1H).

Ejemplo 175

Sal del ácido bis-trifluoroacético de N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-[3-(difluorometoxi)fenil]etil]-4-(aminometil)-trans-ciclohexanocarboxamida

Parte A: Éster de etilo del ácido 2-(Benzhidriliden-amino)-3-(3-difluorometoxi-fenil)-propiónico: El éster etílico de N-(difenilmetilen)glicina (500 mg, 1.87 mmol), bromuro de tetrabuilamonio (63 mg, 0.187 mmol) y bromuro de 3-(difluorometoxi)bencilo (0.5 mL, 1.87 mmol) se colocaron en un matraz. El matraz se evacuó y volvió a rellenar con argón. El diclorometano anhidro se agregó al matraz, y la reacción se enfrió en un baño de acetona con hielo seco a -78°C. La 2-tert-butilimino-2-dietilamino-1,3-dimetilperhidro-1,3,2-diazafosforina (0.7 mL, 2.44 mmol) se

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agregó lentamente bajo argón a -78°C. La reacción se permitió para agitar a -78°C durante 30 minutos, y luego se entibió a temperatura ambiente durante 16 horas. El solvente se removió bajo vacío. El residuo se pre-absorbió en SiO_2 y el producto se aisló por medio de SiO_2 para producir 700 mg de aceite amarillo brillante. EM 424.0 $(M+H)^+$.

Parte B: Éster de etilo del ácido 2-amino-3-(3-difluorometoxi-fenil)-propiónico: El producto del Ejemplo 175 Parte A (700 mg, 1.65 mmol) se colocó en un matraz y se disolvió en THF (30 mL). El ácido cítrico al 30% (p/v) (solución acuosa, 30 mL) se agregó y la reacción se agitó a temperatura ambiente durante 72 horas. La solución se extrajo con éter de dietilo (50 mL), y la capa acuosa se ajustó a un pH 6 usando una solución de $NaHCO_3$ saturada. La solución acuosa se extrajo con diclorometano, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y evaporó para producir 420 mg (97% de rendimiento) de un vidrio claro. EM 260 $(M+H)^+$.

Parte C: Éster de etilo del ácido trans-2-{[4-(tert-butoxicarbonilamino-metil)-ciclohexanocarbonil]-amino}-3-(3-difluorometoxi-fenil)-propiónico: El producto del Ejemplo 175 parte B (420 mg, 1.62 mmol) se trató usando el procedimiento descrito en el Ejemplo 2 parte A para producir 800 mg (97% de rendimiento) de un sólido blanco. EM 497 (M-

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H)⁻.

Parte D: Ácido trans-2-{[4-(tert-Butoxicarbonilamino-metil)-ciclohexanocarbonil]-amino}-3-(3-difluorometoxi-fenil)-propiónico: El producto del Ejemplo 175 parte C (800 mg, 1.6 mmol) se trató de acuerdo con el procedimiento descrito en el Ejemplo 26 para producir 750 mg de un sólido viscoso. EM 469 (M-H+)-.

Parte E: Sal del ácido bis-trifluroracético de [1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(3-difluorometoxi-fenil)-etil]-amida del ácido trans-4-Aminometil-ciclohexanocarboxílico: El producto del Ejemplo 175 parte D (284 mg, 0.6 mmol) se trató secuencialmente de conformidad con los procedimientos descritos en el Ejemplo 1 parte A, Ejemplo 2 Parte B y Ejemplo 120 Parte H para producir 1.1 mg (9% de rendimiento) del compuesto del título como un vidrio transparente después de la purificación por CLAR preparativa. ^{1}H RMN (500 MHz, MeOH-d_4) δ 0.98-1.20 (m, 1H) 1.33 (s, 1H) 1.49-1.65 (m, 1H) 1.74-1.91 (m, J=11.55 Hz, 1H) 2.25 (s, 1H) 2.77 (d, J=7.15 Hz, 1H) 3.16 (s, 1H) 3.55-3.69 (m, 1H) 5.34 (t, J=7.97 Hz, 1H) 6.77 (s, 1H) 7.00 (s, 1H) 7.06 (dd, J=24.74, 8.25 Hz, 1H) 7.33 (t, J=7.97 Hz, 1H) 7.77 (d, J=8.25 Hz, 1H) 7.84 (s, 1H) 7.98 (d, J=8.80 Hz, 1H); EMAR m/z Calculado para $C_{27}H_{32}N_5O_3F_2$ $(M+H)^+$: 512.2473 Encontrado

512.2485.

Ejemplo 176

(S)-3-amino-N-[1-[4-[4-(carbamimidoil)fenil]-1H-imidazol-2-il]-2-feniletil]-1H-indazol-5-carboxamida

Parte A: Sal de diclorohidrato 4-[2-((S)-1-amino-2-fenil-etil)-1H-imidazol-4-il]-benzonitrilo: El éster terc-butílico del ácido {(S)-1-[4-(4-cianofenil)-1H-imidazol-2-il]-2-feniletil}carbámico preparado como se describió en el Ejemplo 28, Parte A (1.0 g, 2.57 mmol) se disolvió en dioxano (10 mL) y el HCl 4 N en dioxano (10 mL) y 5 mL de dioxano adicional se agregaron. La mezcla resultante se agitó durante 2-2.5 horas a temperatura ambiente bajo N_2, luego se diluyó con éter. El sólido resultante se trituró con éter adicional y se colectó por filtración, se lavó con éter y hexano y se secó para proporcionar la sal de diclorohidrato amina como un sólido verde ligero (0.89 g, 96%). ^{1}H RMN (500 MHz, DMSO-D6) δ 3.25-3.32 (m, 1H) 3.33-3.40 (m, 1H) 4.60 (s, 1H) 7.11 (d, J=7.15 Hz, 2H) 7.16-7.29 (m, 3H) 7.78-7.89 (m, 3H) 7.95 (d, J=8.25 Hz, 2H) 8.65 (s, 2H). m/z 289.2 $(M+H)^+$.

Parte B: 3-Ciano-N-{(S)-1-[4-(4-ciano-fenil)-1H-imidazol-2-il]-2-fenil-etil}-4-fluoro-benzamida: Una mezcla del compuesto del Ejemplo 176 Parte A (100 mg, 0.28 mmol), ácido 3-ciano-4-fluorobenzoico (46 mg, 0.28 mmol),

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trietilamina (0.085 mL, 0.61 mmol) y BOP (0.18 g, 0.4 mmol) en THF (5 mL) se agitó a temperatura ambiente durante la noche bajo N_2. La mezcla de reacción se diluyó con agua y se extrajo 3X con EtOAc. Los extractos orgánicos se lavaron con $NaHCO_3$ saturado y salmuera y luego se secaron sobre Na_2SO_4 anhidro, se filtraron y se evaporaron. La cromatografía en gel de sílice (hexano/EtOAc) proporcionó el producto de amida (88 mg, 72%). ^1H RMN (500 MHz, $CDCl_3$) δ 3.41 (dd, J=13.75, 7.15 Hz, 1H) 3.58 (dd, J=13.47, 7.97 Hz, 1H) 5.33 (q, J=7.70 Hz, 1H) 7.01-7.09 (m, 1H) 7.18-7.37 (m, 7H) 7.66 (d, J=8.25 Hz, 2H) 7.85 (d, J=8.25 Hz, 2H) 7.89-7.96 (m, 1H) 7.95-8.03 (m, 1H) 9.74 (s, 1H). m/z 436.1 $(M+H)^+$.

Parte C: {(S)-1-[4-(4-ciano-fenil)-1H-imidazol-2-il]-2-fenil-etil}-amida del ácido 3-Amino-1H-indazol-6-carboxílico: El compuesto del Ejemplo 176 Parte B (86 mg, 0.20 mmol) se disolvió en nBuOH (2 mL) y se agregó exceso de hidrazina (0.1 mL). La mezcla se calentó en un tubo sellado a 160°C durante 10 minutos usando irradiación de microondas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con agua y extrajo con EtOAc (2X). Los extractos orgánicos se lavaron con agua y salmuera, se secaron sobre Na_2SO_4 se filtraron y se evaporaron. El aminoindazol crudo [m/z 448.1 $(M+H)^+$] se usó sin purificación en la siguiente etapa.

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Parte D: {(S)-1-[4-(4-carbamimidoil-fenil)-1H-imidazol-2-il]-2-fenil-etil)-amida del ácido N-3-Amino-1H-indazol-5-carboxílico: El compuesto del Ejemplo 176 Parte C se disolvió en etanol (8 mL) y la solución se agitó en un baño de hielo mientras el HCl (g) se burbujeó a través de la solución durante 10-15 minutos. El matraz se tapó entonces herméticamente y se mantuvo en el refrigerador durante la noche. El matraz se entibió a temperatura ambiente, y los contenidos se agitaron durante 3-4 horas, luego el etanol se evaporó. El residuo resultante se trituró con éter para dar un sólido el cual se colectó por filtración y se secó in vacuo. El imidato así obtenido se volvió a disolver en etanol (5 mL) y se agregó exceso de carbonato de amonio (0.2 g). La mezcla se agitó en un matraz herméticamente tapado durante 48 horas a temperatura ambiente. La mezcla de reacción se diluyó con metanol, se decantó y evaporó hasta secarse. El residuo se volvió a disolver en metanol y se purificó por CLAR C18 preparativa para proporcionar la sal bis TFA del producto de amidina del título como un sólido blanco opaco (85 mg, 61%) después de la evaporación de los solventes. ^{1}H RMN (500 MHz, DMSO-D6) δ 3.35-3.47 (m, 2H) 5.51 (q, J=7.15 Hz, 1H) 7.18 (t, J=7.15 Hz, 1H) 7.21-7.34 (m, 6H) 7.80 (d, J=8.80 Hz, 1H) 7.89 (d, J=8.25 Hz, 2H) 7.99 (d, J=8.80 Hz, 2H) 8.03-8.15 (m, 1H) 8.32 (s, 1H) 8.94 (s, 1H) 9.03 (s, 2H) 9.31 (s, 2H) 11.86 (s, 1H). m/z 465.0 $(M+H)^+$.

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Ejemplo 182

N-{(S)-1-[4-(4-Carbamimidoil-fenil)-1-etil-1H-imidazol-2-il]-2-fenil-etil}-benzamida

Parte A: N-{(S)-1-[4-(4-Ciano-fenil)-1H-imidazol-2-il]-2-fenil-etil}-benzamida: El compuesto del Ejemplo 176 Parte A (0.15 g, 0.42 mmol) se acopló con ácido benzoico usando el procedimiento del Ejemplo 176 Parte B para proporcionar el compuesto del título (0.12 g, 76%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.45-3.65 (m, 2H) 5.34 (d, J=8.35 Hz, 1H) 6.82 (d, J=7.47 Hz, 1H) 7.19-7.35 (m, 7H) 7.40 (t, J=7.69 Hz, 2H) 7.45-7.56 (m, 1H) 7.64 (d, J=7.03 Hz, 4H) 7.86 (d, J=8.35 Hz, 2H). m/z 393.1 $(M+H)^+$.

Parte B: N-{(S)-1-[4-(4-Ciano-fenil)-1-etil-1H-imidazol-2-il]-2-fenil-etil}-benzamida: El compuesto del Ejemplo 182 Parte A (60 mg, 0.15 mmol) se disolvió en DMF (2.5 mL) y carbonato de potasio (32 mg, 0.23 mmol) se agregó seguido por yoduro de etilo (0.015 mL, 0.19 mmol), y la mezcla resultante se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc (3X). Los extractos orgánicos se lavaron con agua y salmuera, luego se secaron sobre Na_2SO_4, se filtraron y evaporaron. El residuo se procesó por cromatografía en gel de sílice para proporcionar el producto (48 mg, 76%). ^{1}H RMN (400 MHz, DMSO-D6) δ 1.17 (t, J=7.25 Hz,

3H) 3.34-3.48 (m, 2H) 3.89-4.05 (m, 2H) 5.46 (d, J=7.03 Hz, 1H) 7.14 (d, J=7.03 Hz, 1H) 7.21 (t, J=7.47 Hz, 2H) 7.31 (d, J=7.47 Hz, 2H) 7.41 (t, J=7.25 Hz, 2H) 7.48 (d, J=7.03 Hz, 1H) 7.76-7.84 (m, 3H) 7.88 (s, 1H) 7.94 (d, J=8.79 Hz, 2H) 9.08 (d, J=8.35 Hz, 1H). m/z 421.2 $(M+H)^+$.

Parte C: N-[(S)-1-[4-(4-Carbamimidoil-fenil)-1-etil-1H-imidazol-2-il]-2-fenil-etil}-benzamida: El compuesto del Ejemplo 182 Parte B (17 mg) se disolvió en etanol (2 mL) y clorohidrato de hidroxilamina (15 mg, 5 eq) y trietilamina (0.03 mL, 5 eq) se agregaron. La mezcla se calentó en un tubo sellado a 125°C durante 15 minutos usando irradiación de microondas. Alícuotas adicionales de clorhidrato de hidroxilamina y trietilamina se agregaron y la irradiación de microondas se repitió durante 10 minutos adicionales a 120°C. El solvente se evaporó, y el residuo se volvió a disolver en ácido acético (2 mL) y se trató con anhídrido acético (0.015 mL, 3 eq). La solución se agitó durante 15 minutos a temperatura ambiente seguido por adición de polvo de zinc (25 mg, 10 eq) y un poco de MeOH. La mezcla se agitó luego durante la noche a temperatura ambiente. La reacción se filtró a través de una almohadilla de Celite y los sólidos se lavaron con MeOH. El filtrado se evaporó, y el residuo se purificó por CLAR C18 preparativa para proporcionar la sal bis-TFA del compuesto del título como un sólido blanco (16

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mg, 60%). ^{1}H RMN (400 MHz, DMSO-D6) δ 1.20 (t, J=7.03 Hz, 3H) 3.33-3.52 (m, 2H) 3.93-4.10 (m, 2H) 5.49 (d, J=7.47 Hz, 1H) 7.16 (t, J=7.47 Hz, 1H) 7.23 (t, J=7.25 Hz, 2H) 7.32 (d, J=7.03 Hz, 2H) 7.43 (t, J=7.47 Hz, 2H) 7.51 (t, J=7.47 Hz, 1H) 7.84 (dd, J=7.69, 5.49 Hz, 4H) 7.95 (s, 1H) 8.00 (d, J=8.35 Hz, 2H) 8.92 (s, 2H) 9.12 (d, J=7.91 Hz, 1H) 9.25 (s, 2H). m/z 450.2 $(M+H)^+$.

Ejemplo 183

N1-{(S)-1-[4-(4-Carbamimidoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-2-fluoro-tereftalamida

Parte A: Éster terc-butílico del ácido ((S)-1-{4-[4-(5-metil-[1,2,4]oxadiazol-3-il)-fenil]-1H-imidazol-2-il}-2-fenil-etil)-carbámico: El éster terc-butílico del ácido {(S)-1-[4-(4-Cianofenil)-1H-imidazol-2-il]-2-feniletil}carbámico se preparó como se describe en el Ejemplo 28 Parte A (1.00 equivalente; 2.57 mmoles; 1.00 g) se disolvió en 15 mL EtOH y clorohidrato de hidroxilamina (12.87 mmoles; 894.42 mg) y trietilamina (12.87 mmoles; 1.79 mL) se agregaron. La solución resultante se calentó a reflujo en un baño de aceite 80°C bajo N_2 durante la noche. La reacción se enfrió a temperatura ambiente y se evaporó para remover el EtOH. El residuo se suspendió en una mezcla de EtOAc/EtOH (~10:1) y se filtró para remover los sólidos inorgánicos. El filtrado se volvió a concentrar hasta una espuma amarilla.

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Este residuo se volvió a disolver en 10 mL HOAc y se trató con agitación bajo N_2 con anhídrido acético (4.23 mmoles; 400 µL). La solución se agitó durante 20 minutos a temperatura ambiente, luego se calentó en un baño de aceite 80°C durante 2 horas, se enfrió a temperatura ambiente y se agitó durante la noche. La mayoría del HOAc se removió en un evaporador rotatorio, luego el residuo se diluyó con agua y se neutralizó cuidadosamente por adición de $NaHCO_3$ saturado a un pH ~8. Se extrajo 3X con CH_2Cl_2. Los extractos combinados se lavaron con salmuera luego se secaron sobre $MgSO_4$, se filtraron y se evaporaron hasta un litro de espuma roja. El residuo se purificó en gel de sílice para proporcionar el producto como un litro de espuma color marrón rosada. (590 mg; 51.4%). ^1H RMN (500 MHz, $CDCl_3$) δ 1.41 (s, 9H) 2.65 (s, 3H) 3.28-3.44 (m, 2H) 4.88 (d, J=7.70 Hz, 1H) 5.23 (s, 1H) 7.13-7.36 (m, 5 H) 7.42-7.55 (m, 1H) 7.88 (d, J=8.25 Hz, 2H) 8.06 (d, J=8.25 Hz, 2H) 9.67 (s, 1H). m/z 446.1 $(M+H)^+$.

Parte B: Diclorohidrato de (S)-1-[4-[4-(5-Metil-[1,2,4]oxadiazol-3-il)-fenil]-1H-imidazol-2-il]-2-fenil-etilamina: El grupo BOC se removió a partir del compuesto del Ejemplo 183 Parte A usando el procedimiento del Ejemplo 176, Parte A para proporcionar la sal de clorohidrato de la amina como un sólido color marrón en 46% de rendimiento. ^1H RMN (500 MHz, $CDCl_3$) δ 2.67 (s, 3H) 2.87 (dd, J=13.75, 9.35 Hz,

1H) 3.44 (dd, J=13.75, 4.40 Hz, 1H) 4.44 (dd, J=9.35, 4.40 Hz, 1H) 7.20-7.31 (m, 5H) 7.34 (t, J=7.42 Hz, 3H) 7.85 (s, 1H) 8.08 (d, J=8.80 Hz, 2H). m/z 346.0 (M+H), 330.0 (M+H-NH3)$^+$.

Parte C: 4-Ciano-2-fluoro-N-((S)-1-{4-[4-(5-metil-[1,2,4]oxadiazol-3-il)-fenil]-1H-imidazol-2-il}-2-fenil-etil)-benzamida: El compuesto del Ejemplo 183 Parte B se acopló al ácido 4-ciano-2-fluorobenzoico usando el procedimiento del Ejemplo 176 Parte B para proporcionar la amida en 90% de rendimiento. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm 2.64 (s, 3H) 3.43 (dd, J=13.75, 7.15 Hz, 1H) 3.58 (dd, J=13.75, 7.70 Hz, 1H) 5.38 (q, J=7.15 Hz, 1H) 7.20-7.33 (m, 7H) 7.42 (d, J=9.90 Hz, 1H) 7.54 (d, J=8.25 Hz, 2H) 7.86 (s, 1H) 8.05 (d, J=8.25 Hz, 2H) 8.14 (t, J=7.70 Hz, 1H) 9.43 (s, 1H). m/z 493.1 (M+H)$^+$.

Parte D: 2-Fluoro-N1-((S)-1-{4-[4-(5-metil-[1,2,4]oxadiazol-3-il)-fenil]-1H-imidazol-2-il}-2-fenil-etil)-tereftalamida: Una mezcla del compuesto del Ejemplo 183 Parte C (75 mg, 0.15 mmol), carbonato de potasio (66 mg, 3 eq) y peróxido de hidrógeno al 30% (0.055 mL, 11 eq) en DMSO (2.5 mL) se agitó a temperatura ambiente bajo N_2 durante la noche. La mezcla de reacción se diluyó con agua y EtOAc, y las fases se separaron. La fase acuosa se volvió a extraer

con EtOAc (2X). Las fases orgánicas combinadas se lavaron con agua y salmuera, se secaron sobre Na_2SO_4 anhidro, se filtraron y evaporaron. La amida cruda resultante se usó sin purificación. m/z 511.0 $(M+H)^+$.

Parte E: N1-{(S)-1-[4-(4-Carbamimidoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-2-fluoro-tereftalamida: El compuesto del Ejemplo 183 Parte D (68 mg) y Pd/C al 10% (35 mg, húmedo, Degussa) se suspendieron en una mezcla de metanol y trietilamina (4.5 ml, 8:1) y se agitó bajo 1 atmósfera de H_2 durante la noche. El catalizador se removió por filtración a través de Celite y se lavó con MeOH. El filtrado se evaporó y el residuo se purificó por CLAR C18 preparativa para proporcionar la sal bis TFA del compuesto del título como un sólido blanco (48 mg, 53%). ^1H RMN (500 MHz, DMSO-D6) δ ppm 3.23-3.31 (m, 1H) 3.41 (dd, J=13.75, 6.60 Hz, 1H) 5.43 (q, J=7.70 Hz, 1H) 7.13-7.23 (m, 1H) 7.23-7.31 (m, 5H) 7.59-7.66 (m, 2H) 7.67-7.77 (m, 2H) 7.87 (t, J=7.70 Hz, 2H) 7.99 (d, J=8.25 Hz, 3H) 8.13 (s, 1H) 8.95 (s, 2H) 8.98-9.06 (m, 1H) 9.27 (s, 2H). m/z 471.0 $(M+H)^+$.

Ejemplo 188

Sal del ácido bis-trifluoroacético de N1-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-2-fluorotereftalamida

El Ejemplo 188 se preparó similarmente por

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aplicación apropiada de los procedimientos descritos por el Ejemplo 120, donde ácido 4-carbamoil-2-fluorobenzoico en lugar de ácido Boc-tranexámico se usó en el Ejemplo 120 Parte F. ^{1}H-RMN (500 MHz, DMSO-d6) δ 3.16 (dd, J = 13.75, 8.80 Hz, 1H), 3.30 (dd, J = 13.75, 6.05 Hz, 1H) 5.31-5.43 (m, 1H), 7.16-7.23 (m, 1H), 7.25-7.31 (m, 5H), 7.38 (d, J = 8.80 Hz, 1H), 7.55 (t, J = 7.42 Hz, 1H), 7.62 (d, J = 5.50 Hz, 2H), 7.65-7.76 (m, 2H), 7.86 (d, J = 8.80 Hz, 1H), 8.12 (s, 1H), 8.97 (d, J = 8.25 Hz, 2H), 12.05 (s, 1H), 12.81 (s, 1H).

Ejemplo 189

Sal del ácido bis-trifluoroacético de N1-((S)-1-(4-(4-aminoquinazolin-7-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-2-fluorotereftalamida

El Ejemplo 189 se preparó por aplicación apropiada de los procedimientos por el Ejemplo 162, excluyendo el Ejemplo 162 Parte G y usando ácido 4-carbamoil-2-fluorobenzoico en lugar de ácido Boc-tranexámico en el procedimiento del Ejemplo 120 Parte F. EM: 530.01, $(M+H)^+$. ^{1}HRMN (500 MHz, DMSO-d_6) δ 3.14-3.24 (m, 1H), 3.25-3.35 (m, 1H,) 5.31-5.44 (m, 1H), 7.15-7.24 (m, 1H), 7.24-7.33 (m, 5H), 7.54 (t, J = 7.70 Hz, 1H), 7.64 (s, 1H), 7.66-7.76 (m, 3H), 7.99 (d, J = 8.80 Hz, 1H), 8.13 (s, 2H), 8.46 (d, J = 8.80 Hz, 1H), 8.80 (s, 1H), 9.07 (d, J = 6.60 Hz, 1H), 13.20 (s, 1H).

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Ejemplo 190

Sal del ácido bis-trifluoroacético de 1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-5,6,7,8-tetrahidroisoquinolin-6-carboxamida

El Ejemplo 190 se preparó similarmente por la aplicación apropiada de los procedimientos por el Ejemplo 147 Parte H usando el diaestereómero B de la Parte G del Ejemplo 147. ^{1}H-RMN (400 MHz, d_4-MeOH) δ 1.75 (dd, J = 13.40, 10.33 Hz, 1H), 2.01 (m, 1H), 2.45 (t, J = 6.37 Hz, 2H), 2.73 (m, 1H), 2.90 (m, 2H), 3.20 (m, 2H), 5.28 (m, 1H), 6.69 (d, J = 6.59 Hz, 1H), 7.25 (m, 5H), 7.51 (d, J = 8.79 Hz, 1H), 7.59 (d, J = 6.59 Hz, 1H), 7.71 (s, 1H), 7.95 (d, J = 8.79 Hz, 1H).

Ejemplo 191

Sal del ácido bis-trifluoroacético de 1-amino-N-((S)-1-(4-(4-aminoquinazolin-7-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-5,6,7,8-tetrahidroisoquinolin-6-carboxamida

El Ejemplo 191 se preparó usando el producto de la Parte F del Ejemplo 147 por la aplicación apropiada de los procedimientos descritos en la Parte A del Ejemplo 162. CL/EM: 539.2 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 1.77 (m, 1H), 2.00 (d, J = 3.95 Hz, 1H,) 2.45 (m, 2H), 2.74 (m, 2H,) 2.91 (m, 1H), 3.21 (m, 2H), 5.26 (m, 1H), 6.67 (t, J = 7.25 Hz, 1H), 7.23 (m, 5H), 7.59 (t, J = 6.59 Hz, 1H), 8.02 (m, 1H),

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8.16 (d, J = 4.39 Hz, 1H), 8.36 (dd, J = 8.79 y 1.76 Hz, 1H), 8.65 (s, 1H).

Ejemplo 192

Sal del ácido bis-trifluoroacético de 1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-3-metilisoquinolin-6-carboxamida

Parte A: Ácido (Z)-3-(3-bromofenil)-2-metilacrílico: El 3-bromobenciladelhído (2.6 g, 0.014 mol) y (carbetoxietiliden)trifenilfosforano (5.6 g, 0.015 mol) se agregaron junto con 30 mL de tolueno. La mezcla se agitó a temperatura ambiente bajo N_2 durante 24 horas. El solvente se removió. El residuo se disolvió en EtOAc y se lavó con agua y salmuera. Esto se secó sobre $MgSO_4$, se concentró, y se purificó por cromatografía instantánea (sílice, Hexano/EtOAc) para dar 3.7 g del éster deseado. EM: 271.2/273.2 $(M+1)^+$. El éster se disolvió luego en 30 mL de THF y 10 mL de agua. El LiOH (1.32 g, 0.031 mol) se agregó. La mezcla se agitó a temperatura ambiente bajo N_2 durante 72 horas. El THF se removió. La mezcla resultante se diluyó con agua y se extrajo con EtOAc (descartado). La mezcla acuosa se acidificó con HCl y se extrajo con EtOAc. Este extracto de EtOAc se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró a un sólido blanco (3.2 g). ^{1}HRMN (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 7.29 (m, 2H), 7.47 (d, J = 7.91 Hz, 1H), 7.56 (s, 1H), 7.73 (s,

1H).

Parte B: 6-Bromo-3-metilisoquinolin-1(2H)-ona: El producto del Ejemplo 192 Parte A (2.76 g, 11.45 mmol) y trietilamina (3.60 mL, 22.90 mmol) se agregaron junto con 18 mL de acetona. La mezcla se enfrió a 0°C, seguido por la adición gota a gota de cloroformiato de etilo (1.85 mL, 17.17 mmol). La mezcla de reacción se agitó a 0-5°C bajo N_2 durante 1 hora. A esto se agregó la mezcla espesa de la azida de sodio (1.34 g, 20.60 mmol) en 2 mL de agua. La mezcla de reacción se agitó a temperatura ambiente bajo N_2 durante la noche. El solvente se removió. El residuo se disolvió en EtOAc y se lavó con agua y salmuera. Esto se secó sobre $MgSO_4$, se concentró, y se secó in vacuo para dar 3.4 g de 80% de azida de acilo deseada. Una solución de tributilamina (4.40 mL, 18.49 mmol) y difenilmetano (15 mL) se calentó a 190°C. A esto se agregó gota a gota la solución de azida de acilo (3.4 g de 80% de material puro, 10.3 mmol) en difenilmetano (12 mL) durante 12 minutos. La mezcla se agitó a 220°C durante 2 horas bajo N_2. Esto se enfrió a temperatura ambiente. El producto crudo se precipitó y filtró. Esto se purificó por cromatografía instantánea (120 g sílice, 0-10% MeOH en diclorometano) para dar 0.43 g del producto deseado. EM: 238.2, 240.1 $(M+1)^+$. ^{1}HRMN (400 MHz, DMSO-d_6) δ 2.20 (s, 3H), 6.30 (s, 1H), 7.52 (d, J = 8.79 Hz, 1H), 7.80 (s, 1H),

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7.81 (d, J = 8.35 Hz, 1H).

Parte C: 6-Bromo-3-metilisoquinolin-1-amina: El oxicloruro de fósforo (2.5 mL) se enfrió en un baño de hielo y se agregó luego gota a gota al producto a partir del Ejemplo 192 Parte B (120 mg, 0.5 mmol). La mezcla se calentó a 110°C bajo N_2 durante 1.5 horas. La reacción se enfrió, y apagó con agua y MeOH. Entonces más agua se agregó. El sólido se filtró y se lavó con NaOH 1N y agua para dar 115 mg de un sólido. El sólido obtenido (51 mg) se combinó con 1 mL de 13-15% NH_3 en etilen glicol. La mezcla se calentó en un tubo sellado por medio de irradiación de microondas a 170°C durante 20 minutos. La reacción se enfrió y se agregó agua. El sólido se filtró y purificó por cromatografía instantánea ISCO (sílice, CH_2Cl_2/MeOH) para dar 12 mg del producto deseado. EM: 237.1/239.1 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 2.39 (s, 3H), 6.76 (s, 1H), 7.53 (m, 1H), 7.81 (d, J = 1.76 Hz, 1H), 7.98 (d, J = 8.79 Hz, 1H).

Parte D: 1-Amino-3-metilisoquinolin-6-carbonitrilo: El producto del Ejemplo 192 Parte C (22 mg, 0.093 mmol), $Zn(CN)_2$ (12 mg), y $Pd(PPh_3)_4$ (8 mg) se agregaron con 2 mL de DMF. La mezcla se calentó en un tubo sellado en microondas a 180°C durante 10 minutos. La mezcla se filtró y se lavó con EtOAc. El filtrado se concentró, y se purificó por

cromatografía instantánea (sílice, CH_2Cl_2/MeOH) para dar 12 mg del producto deseado. CL/EM: 184.18 $(M+1)^+$.

Parte E: Ácido 1-amino-3-metilisoquinolin-6-carboxílico: El producto del Ejemplo 192 Parte D (35 mg) se agregó con 4 mL de MeOH y 4 mL de NaOH acuoso al 15%. La mezcla se calentó a 70-85°C durante 2 horas. Esto se concentró, se hizo ácido con HCl y TFA a un pH = 5. El sólido se filtró y se purificó por CLAR preparativa de fase inversa para dar 18 mg de la sal TFA. CL/EM: 203.03 $(M+1)^+$.

Parte F: Sal del ácido bis-trifluoroacético de 1-amino-N-((S)-1-(4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il)-2-feniletil)-3-metilisoquinolin-6-carboxamida: El producto del Ejemplo 192 Parte E y el producto a partir de la Parte E del Ejemplo 120 se acoplaron y luego se convirtieron a la aminoindazol usando los métodos descritos en el Ejemplo 120 Parte F y Parte H, respectivamente. EM: 537.0 $(M+1)^+$. ^{1}HRMN (400 MHz, d_4-MeOH) δ 2.52 (s, 3H), 3.41 (m, 2H), 5.46 (t, J = 7.91 Hz, 1H), 7.05 (s, 1H), 7.23 (m, 5H), 7.50 (d, J = 8.79 Hz, 1H) 7.71 (s, 1H), 7.98 (m, 2H), 8.19 (s, 1H), 8.43 (d, J = 8.79 Hz, 1H).

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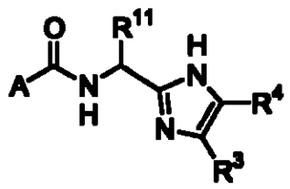
Ejemplo 200

Sal del ácido bis-trifluoroacético de {(S)-2-[4-(3-Amino-1H-indazol-6-il)-1H-imidazol-2-il]-1-bencil-etil}-amida del ácido 4-aminometil-ciclohexancarboxílico

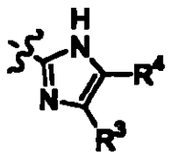
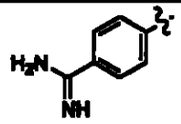
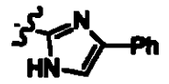
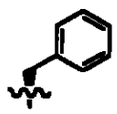
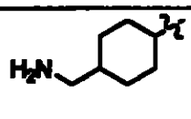
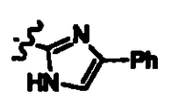
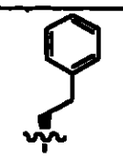
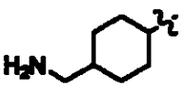
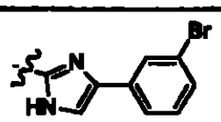
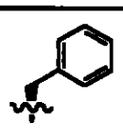
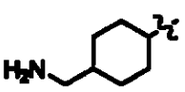
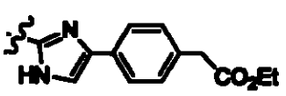
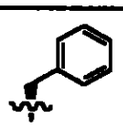
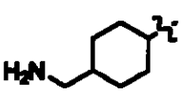
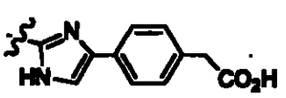
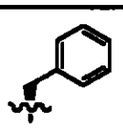
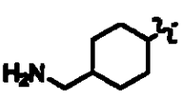
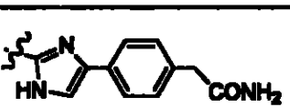
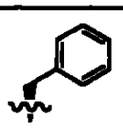
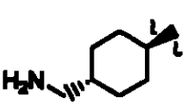
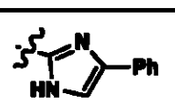
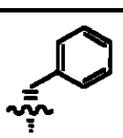
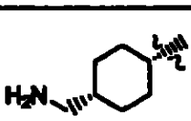
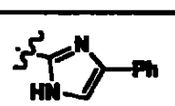
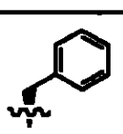
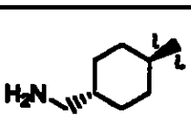
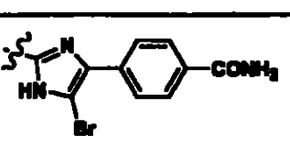
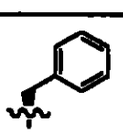
Este compuesto se preparó siguiendo los procedimientos descritos en el Ejemplo 120: ^{1}H RMN (500 MHz, Solvente) δ 0.90-1.01 (m, 2H), 1.18-1.24 (m, 2H), 1.42-1.50 (m, 1H), 1.50-1.62 (m, 2H), 1.68-1.79 (m, 2H), 2.00-2.09 (m, 1H), 2.71 (d, J=7.15 Hz, 2H), 2.94 (dd, J=13.00, 8.80 Hz, 2H), 3.02 (dd, J=13.00, 6.04 Hz, 2H), 3.13 (dd, J=15.12, 10.17 Hz, 1H), 4.57-4.65 (m, 1H), 7.18-7.23 (m, 1H), 7.26-7.30 (m, 4H), 7.47 (d, J=9.90 Hz, 1H), 7.74 (s, 1H) 7.89 (s, 1H), 7.97 (d, J=8.25 Hz, 1H). EMAR (ES$^+$): Calculado para $C_{27}H_{33}N_7O$: 471.2747, Encontrado: 472.2839 (M+H).

Las Tablas 1-6 de abajo resumen los ejemplos preparados de los compuestos en la presente invención.

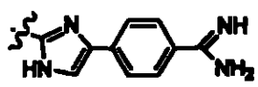
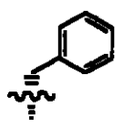
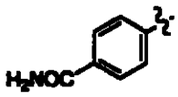
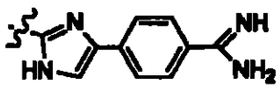
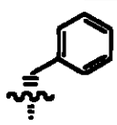
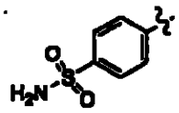
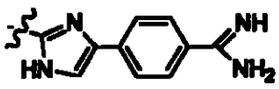
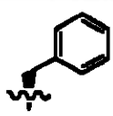
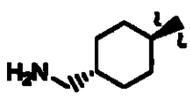
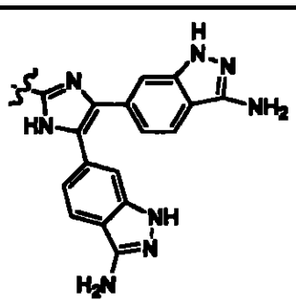
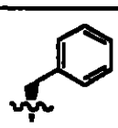
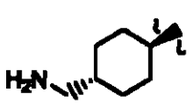
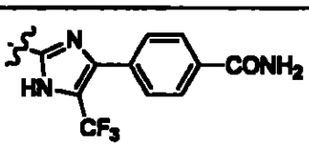
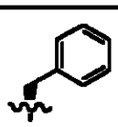
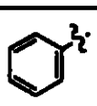
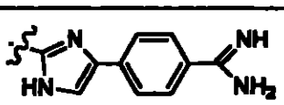
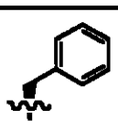
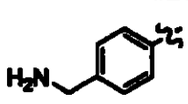
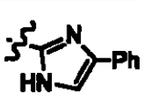
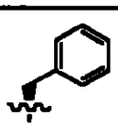
Tabla 1

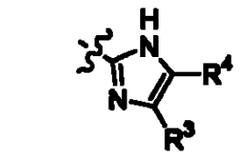
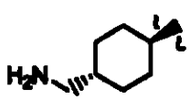
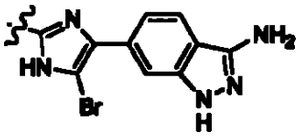
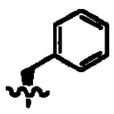
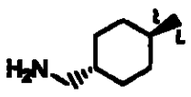
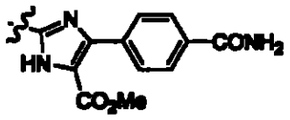
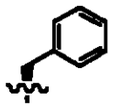
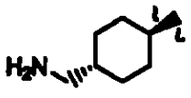
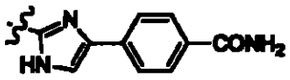
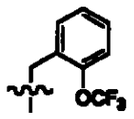
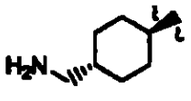
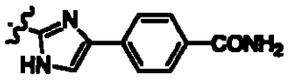
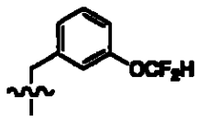
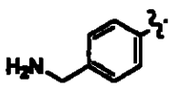
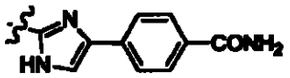
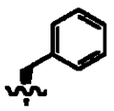
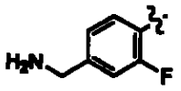
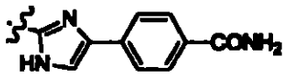
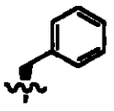
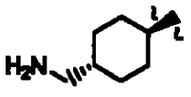
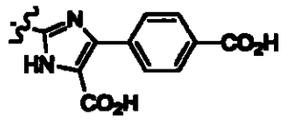
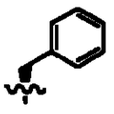
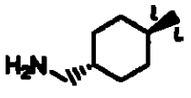
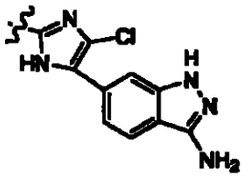


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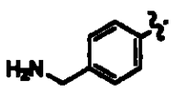
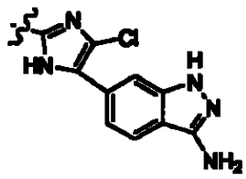
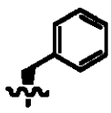
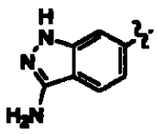
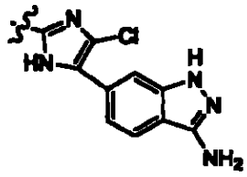
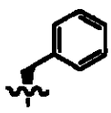
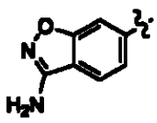
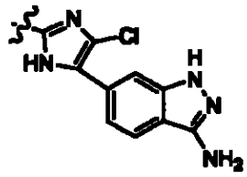
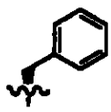
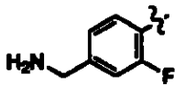
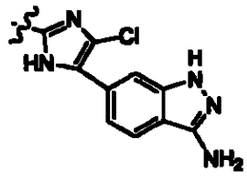
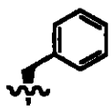
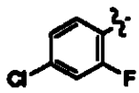
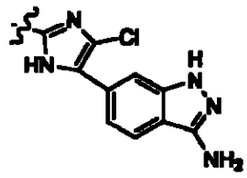
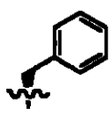
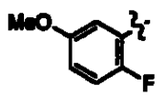
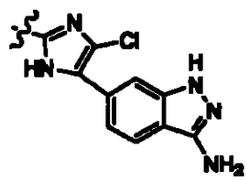
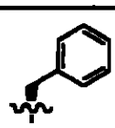
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
1				410.20
14				417.27
15				483.07, 481.07
25				489.29
26				461.26
27				460.27
75				403.2
76				403.1
82				526.1, 524.1

610

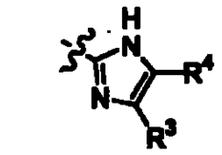
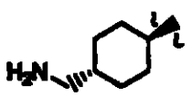
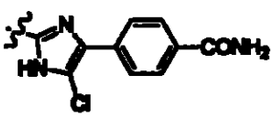
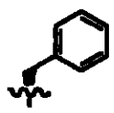
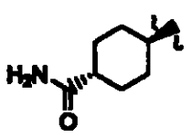
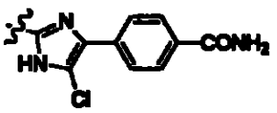
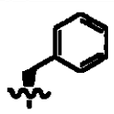
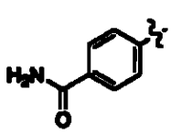
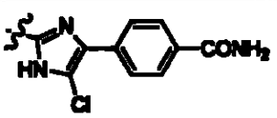
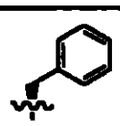
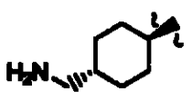
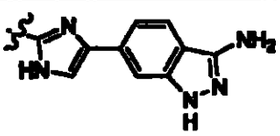
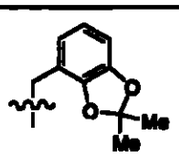
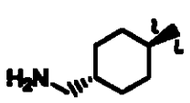
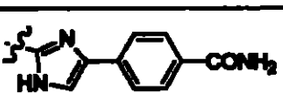
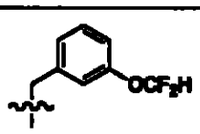
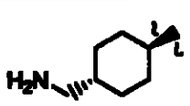
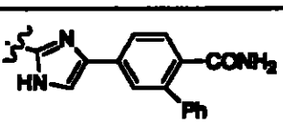
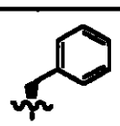
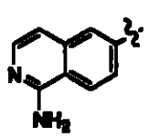
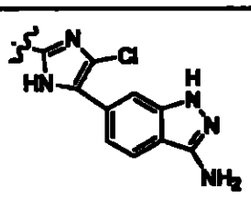
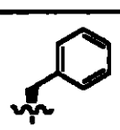
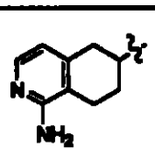
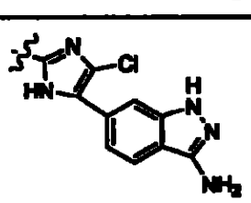
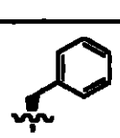
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
83				410.2
84				453.2
86				489.2
106				589.5
107				514.2
108				410.2
112				397.4

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
113				538.4
114				504.4
115				530.2
116				512.3
117				440.2
118				458.2
119				491.2
120				492.4

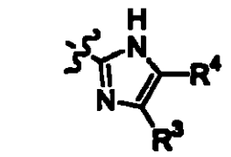
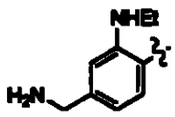
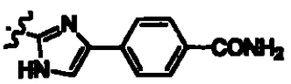
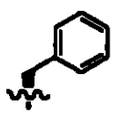
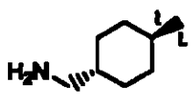
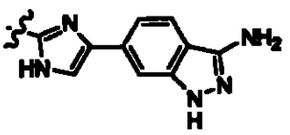
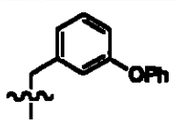
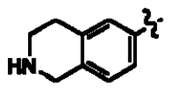
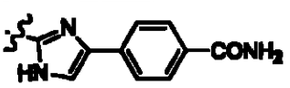
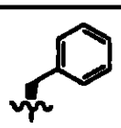
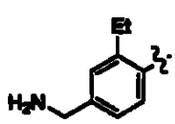
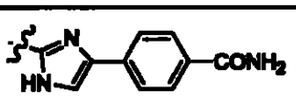
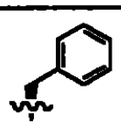
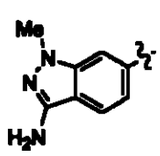
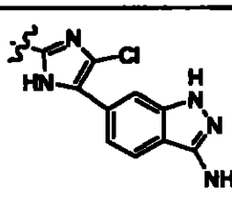
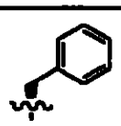
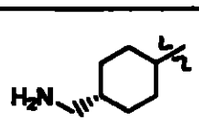
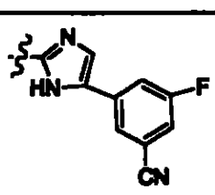
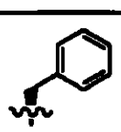
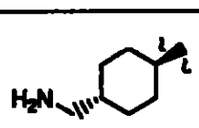
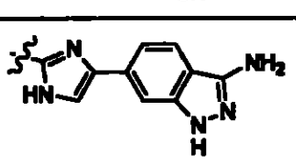
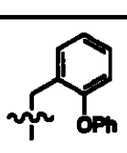
612

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
121				486.3
122				510.3 (M-H+)-
123				513.1
124				504.1
128				509.3
129				505.3

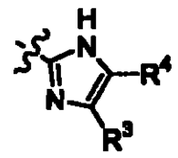
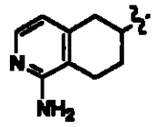
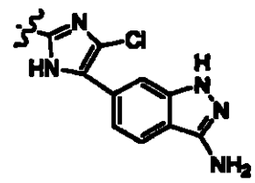
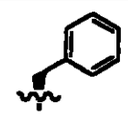
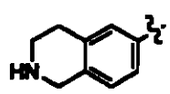
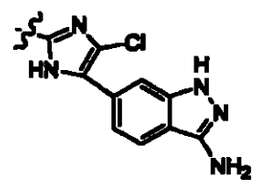
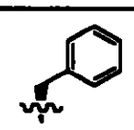
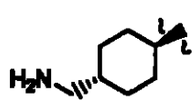
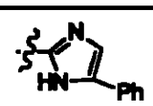
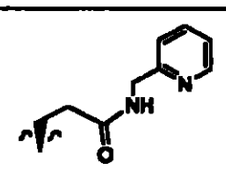
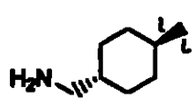
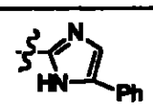
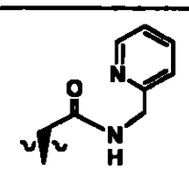
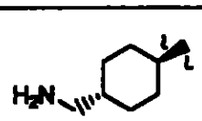
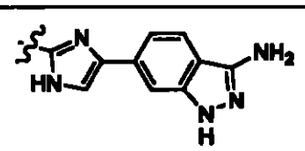
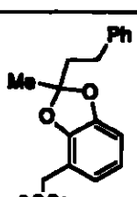
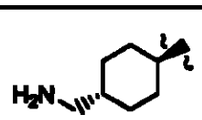
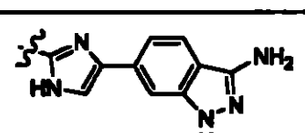
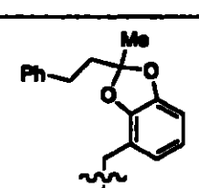
613

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
130				480.4
131				506.2
132				500.1
133				530.3
134				512.1
135				522.4
136				523.2
137				527.3

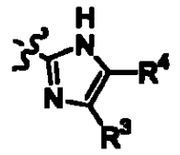
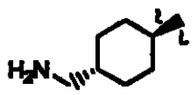
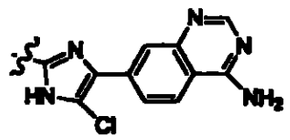
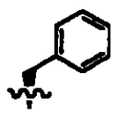
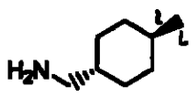
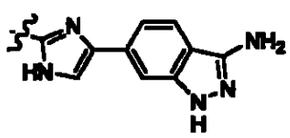
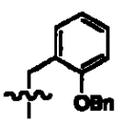
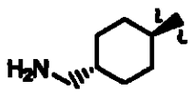
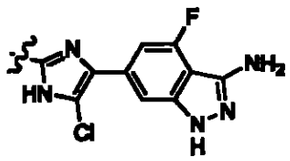
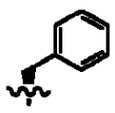
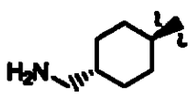
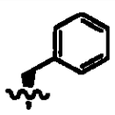
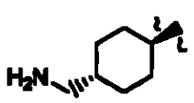
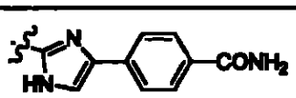
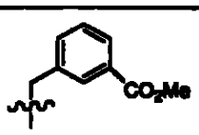
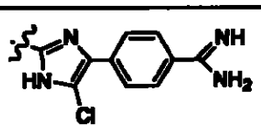
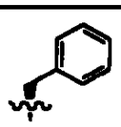
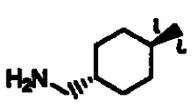
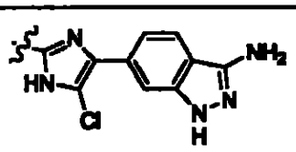
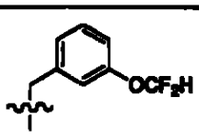
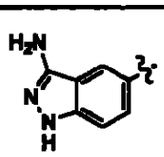
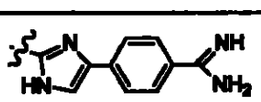
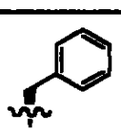
614

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
140				483.4
141				550.3
142				466.2
143				468.4
144				526.3
145				446.3
146				550.2

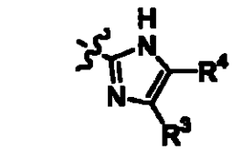
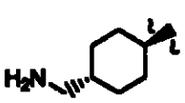
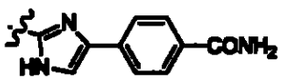
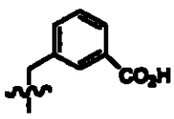
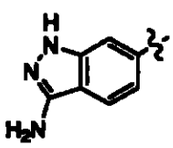
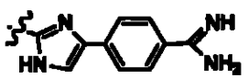
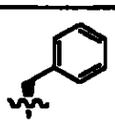
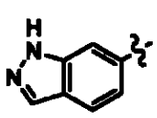
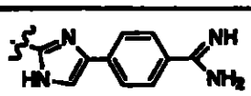
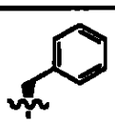
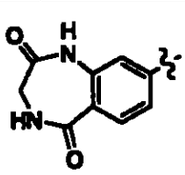
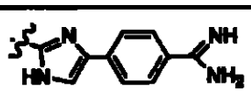
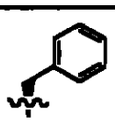
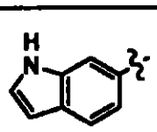
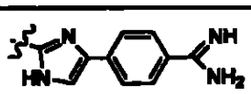
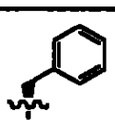
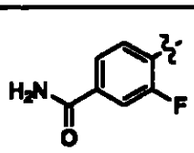
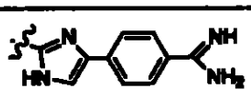
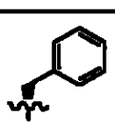
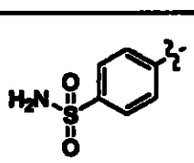
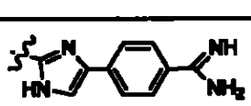
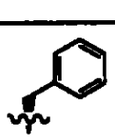
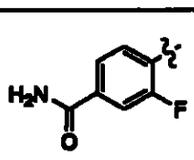
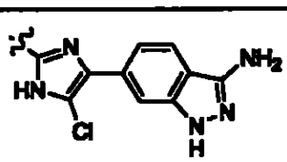
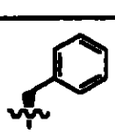
615

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
147				527.3
155				512.2
157				530.3
158				461.3
160				620.3
161				620.3

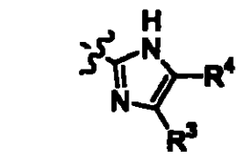
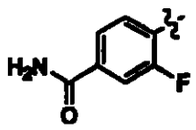
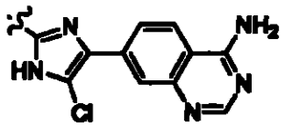
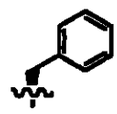
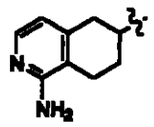
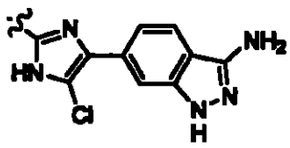
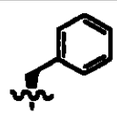
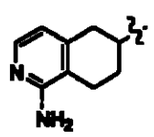
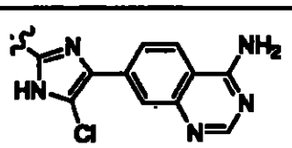
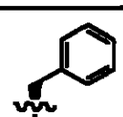
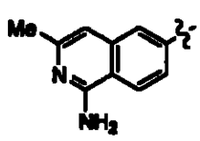
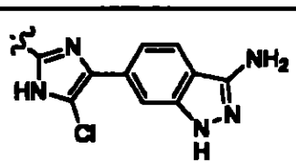
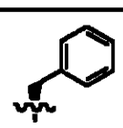
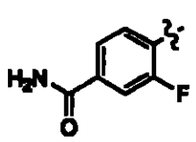
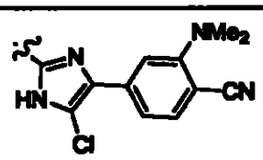
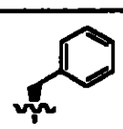
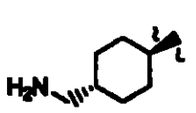
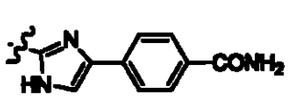
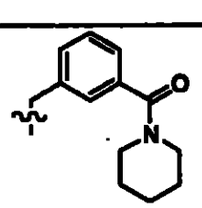
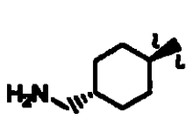
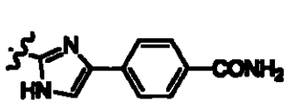
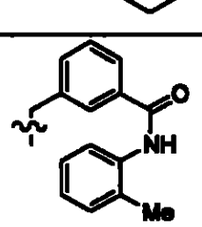
616

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
162				504.2
165				564.0
171				510.3
172				510.3
173				504.1
174				442.2
175				558.2
176				465.0

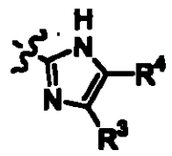
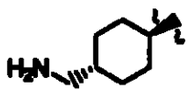
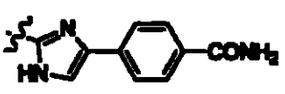
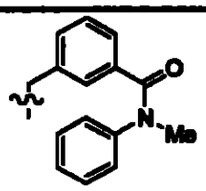
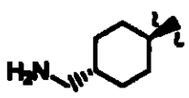
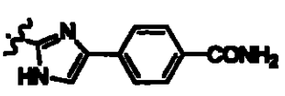
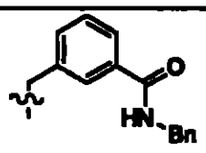
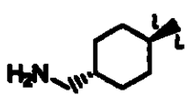
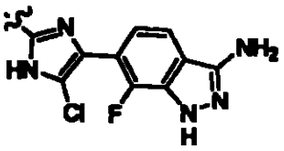
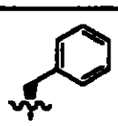
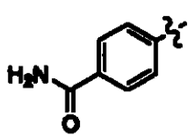
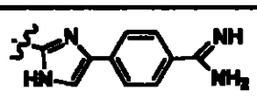
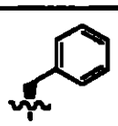
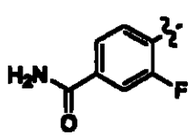
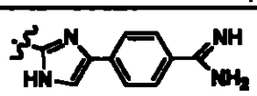
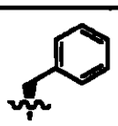
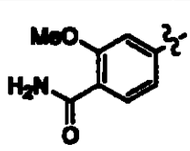
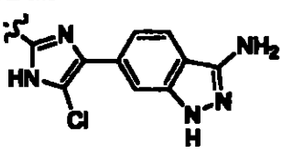
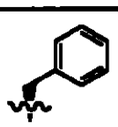
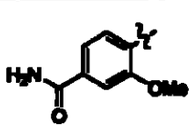
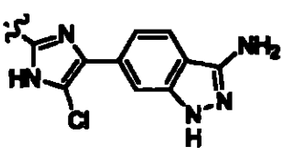
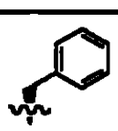
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# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
177				490.0
178				465.0
179				450.0
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181				449.0
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187				489.0
188				518.2

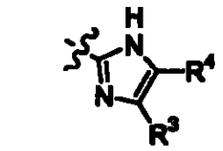
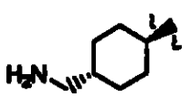
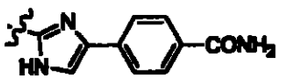
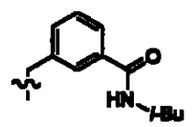
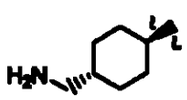
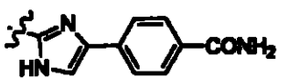
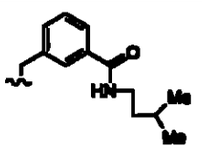
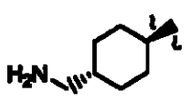
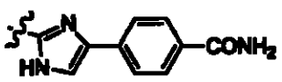
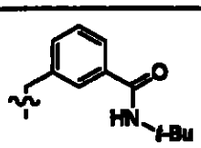
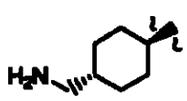
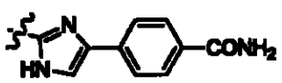
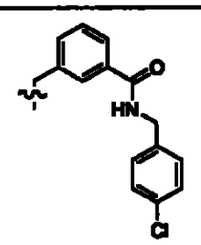
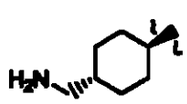
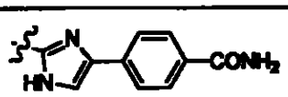
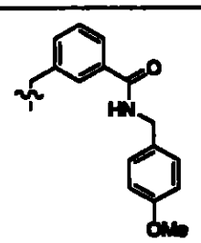
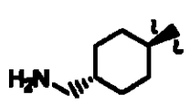
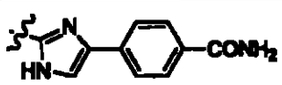
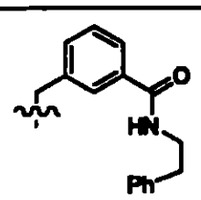
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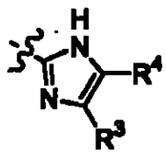
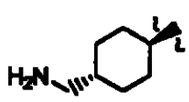
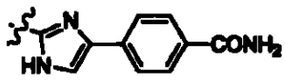
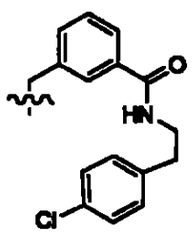
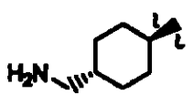
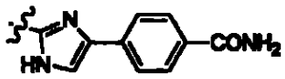
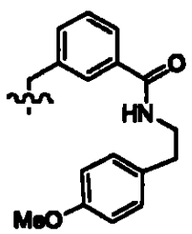
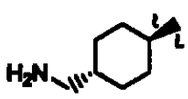
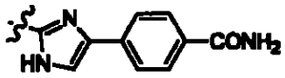
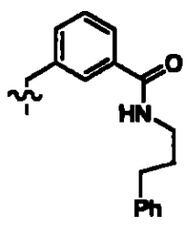
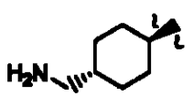
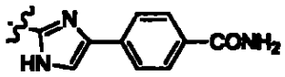
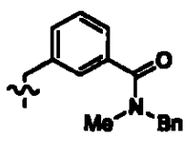
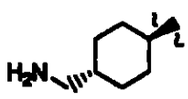
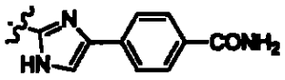
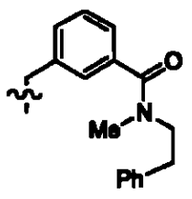
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
189				530.0
190				527.2
191				539.2
192				537.0
194				531.06
195				557.32
196				579.33

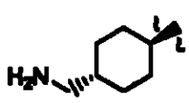
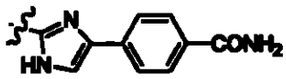
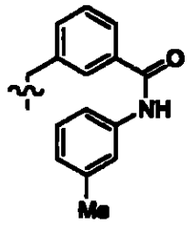
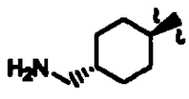
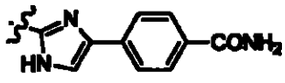
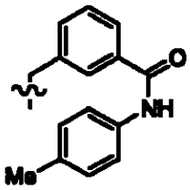
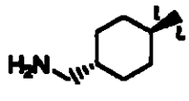
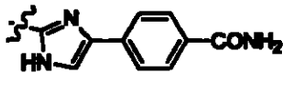
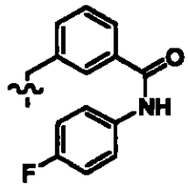
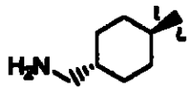
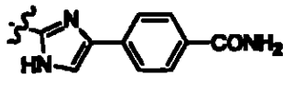
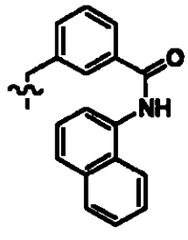
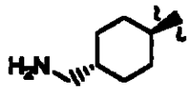
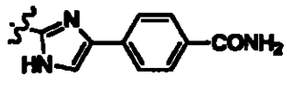
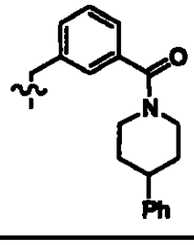
619

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
197				579.31
198				579.35
199				510.3
203				453.0
213				471.03
214				530.17
215				530.17

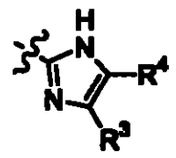
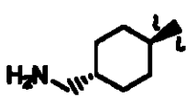
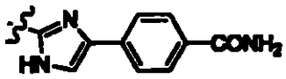
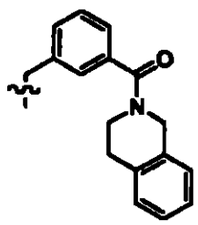
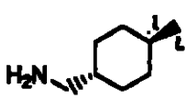
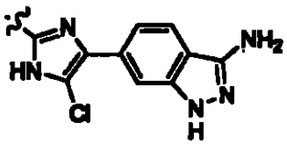
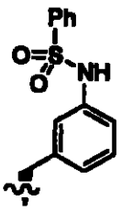
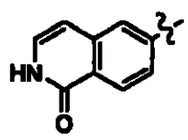
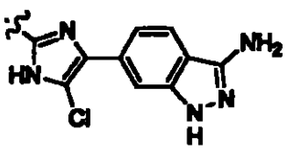
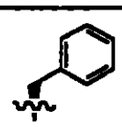
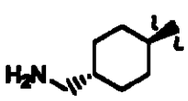
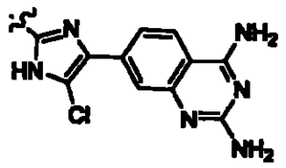
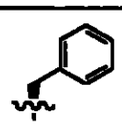
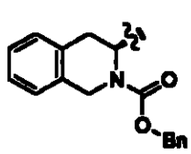
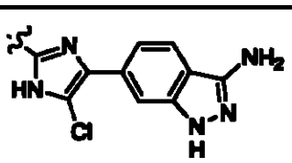
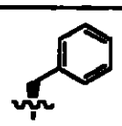
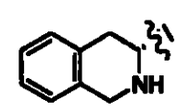
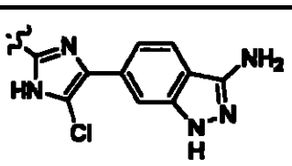
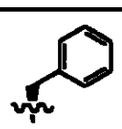
620

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
217				545.3
218				559.32
219				545.4
220				613.3
221				609.32
222				593.35

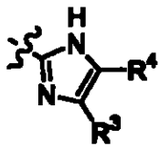
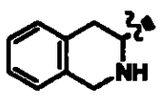
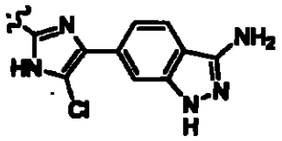
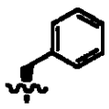
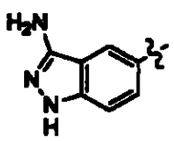
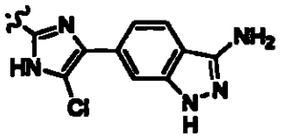
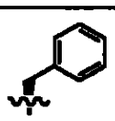
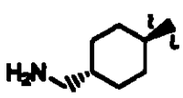
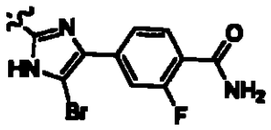
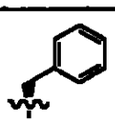
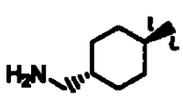
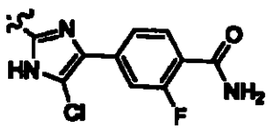
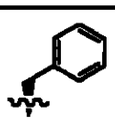
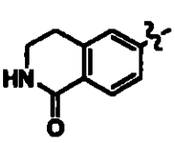
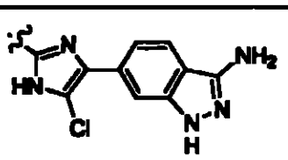
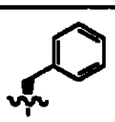
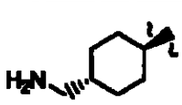
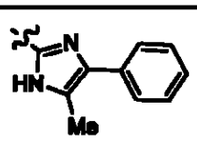
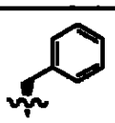
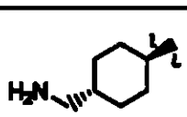
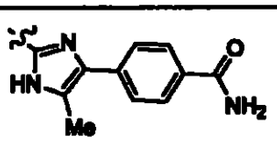
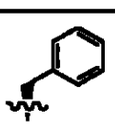
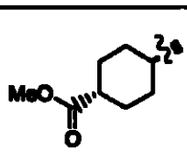
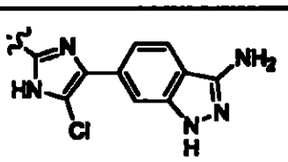
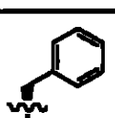
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
223				627.25
224				623.38
225				607.39
226				593.33
227				607.38

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
228				579.3
229				579.36
230				583.31
231				615.36
232				633.45

623

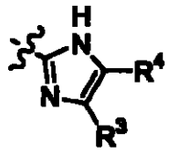
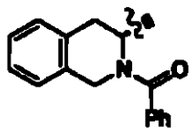
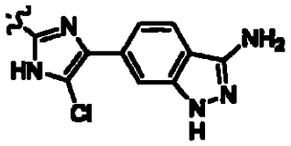
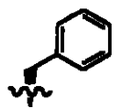
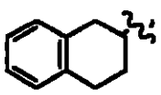
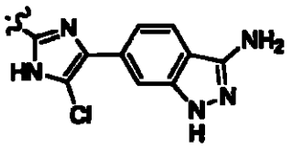
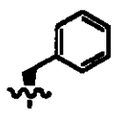
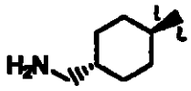
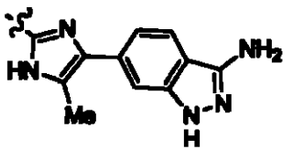
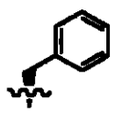
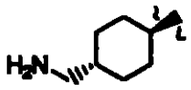
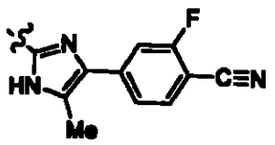
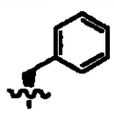
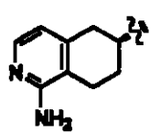
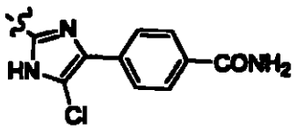
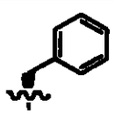
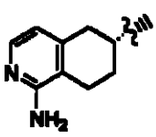
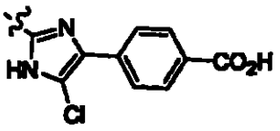
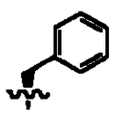
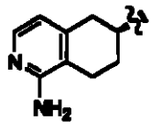
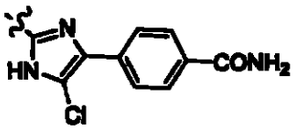
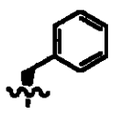
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
233				605.38
235				648.8
238				524.1
239				519.19
241				646.36
242				512.20

624

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
243				512.20
244				512.01
248				542.2
249				498.3
250				526.2
251				417.4
252				460.3
253				521.2

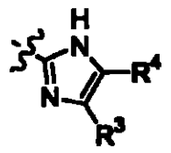
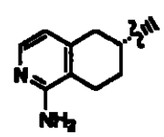
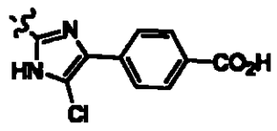
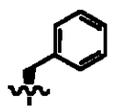
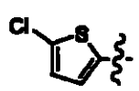
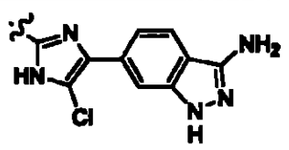
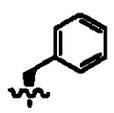
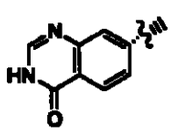
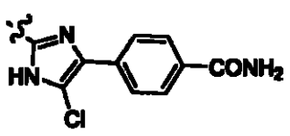
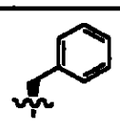
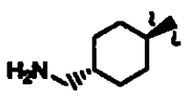
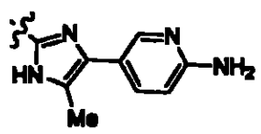
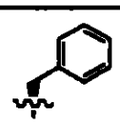
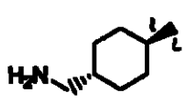
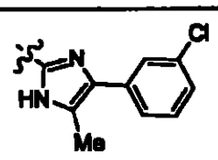
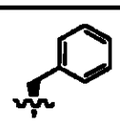
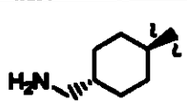
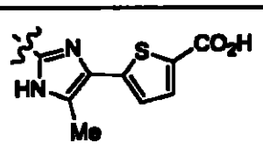
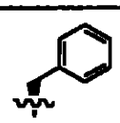
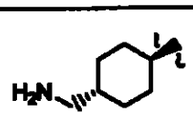
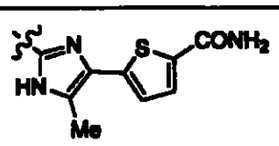
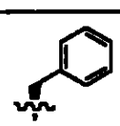
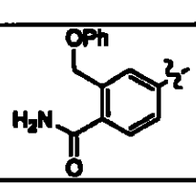
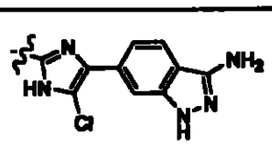
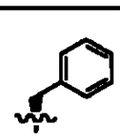
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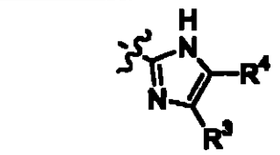
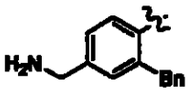
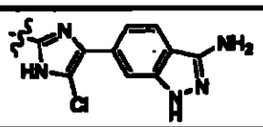
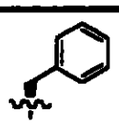
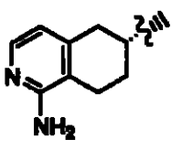
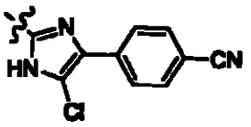
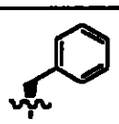
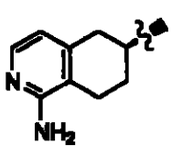
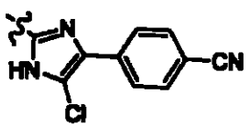
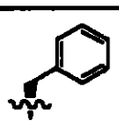
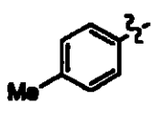
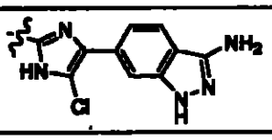
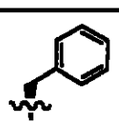
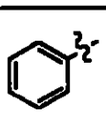
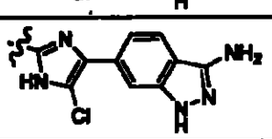
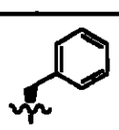
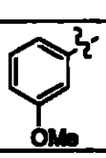
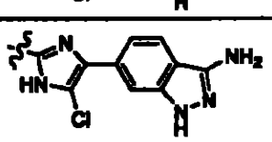
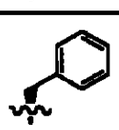
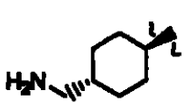
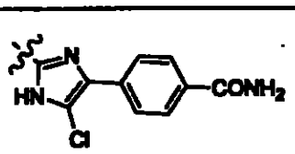
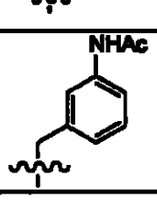
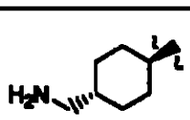
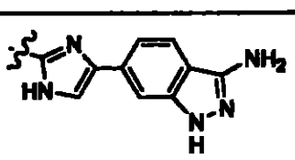
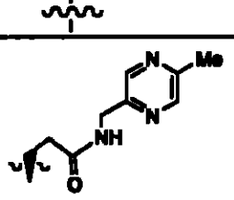
625

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
254				616.2
255				511.2
256				472.4
257				460.4
261				516.2
262				516.2
263				515.2

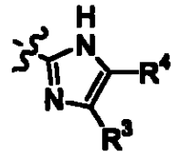
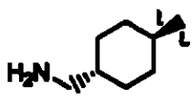
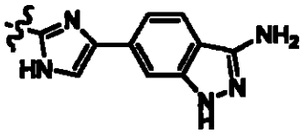
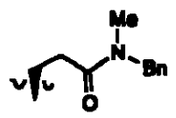
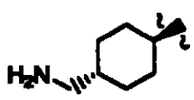
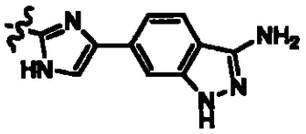
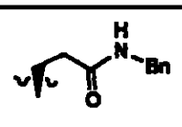
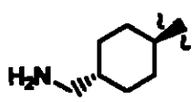
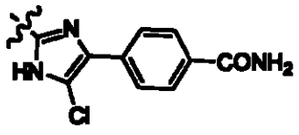
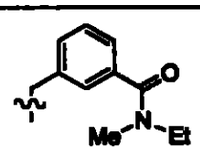
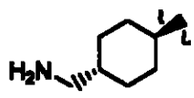
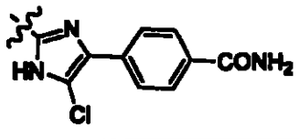
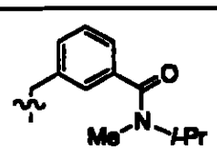
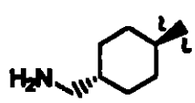
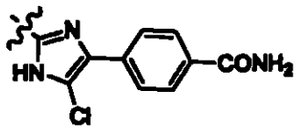
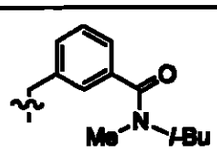
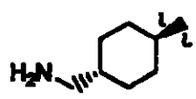
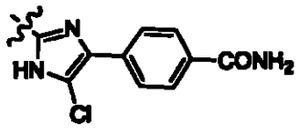
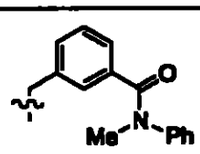
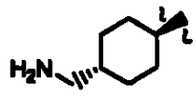
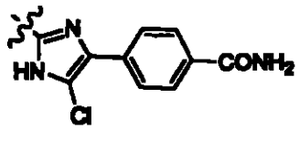
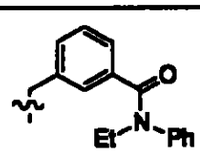
627

626

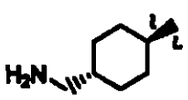
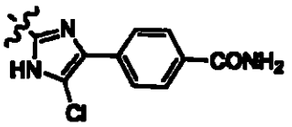
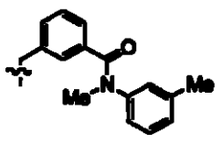
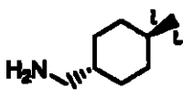
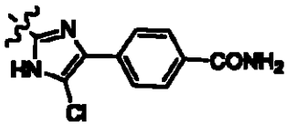
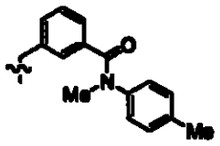
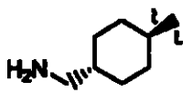
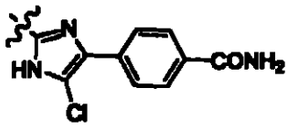
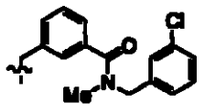
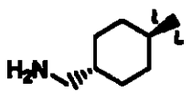
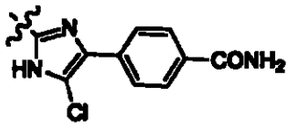
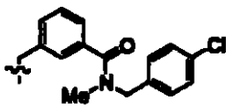
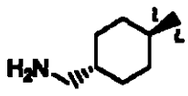
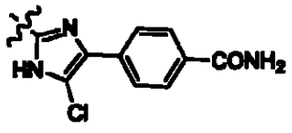
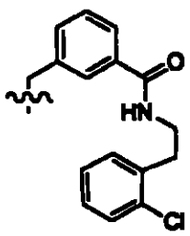
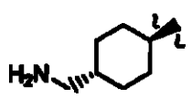
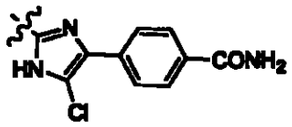
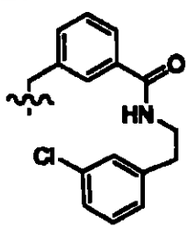
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
264				515.3
265				497.1
266				525.2
267				433.3
268				451.3
269				467.2
270				466.3
271				606.1

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
272				579.2
273				497.2
274				497.2
275				471.3
276				457.3
277				487.3
278				537.2
279				545.3

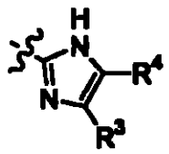
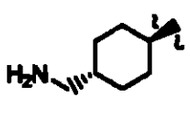
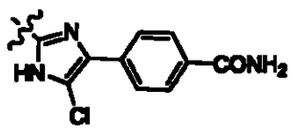
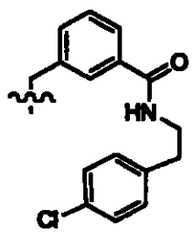
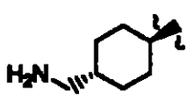
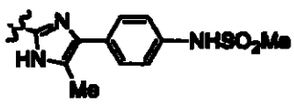
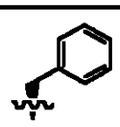
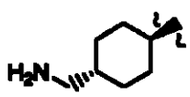
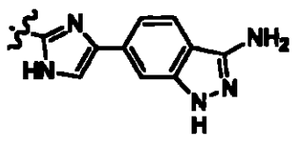
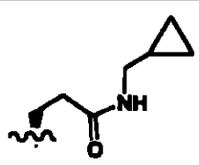
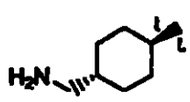
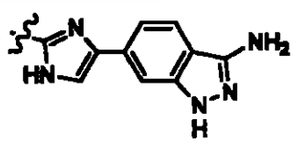
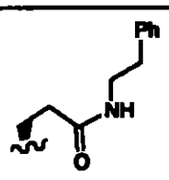
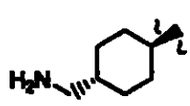
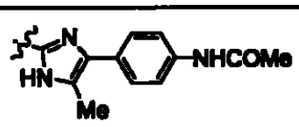
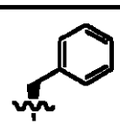
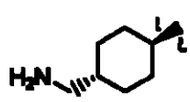
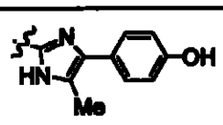
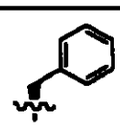
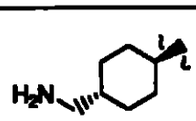
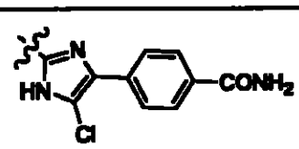
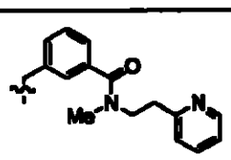
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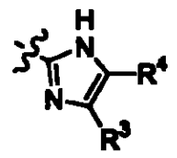
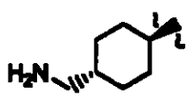
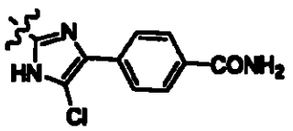
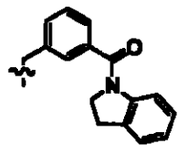
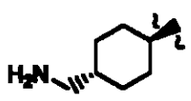
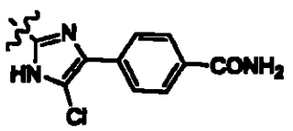
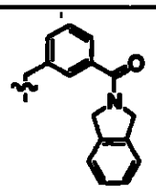
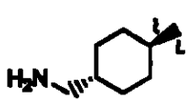
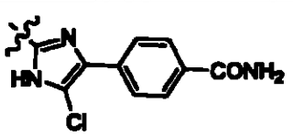
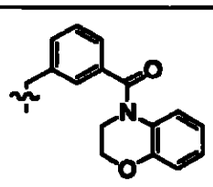
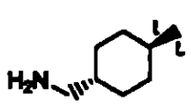
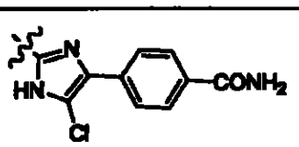
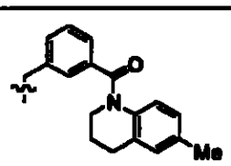
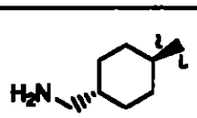
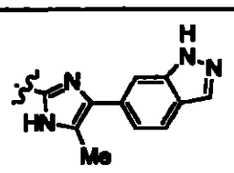
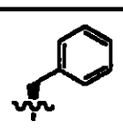
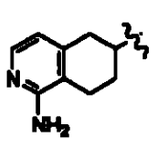
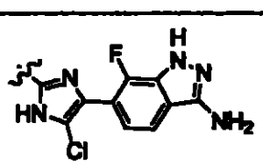
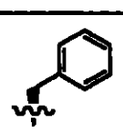
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
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629

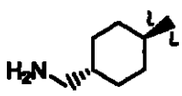
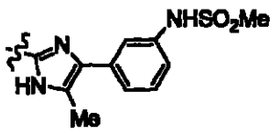
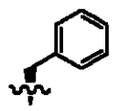
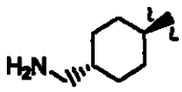
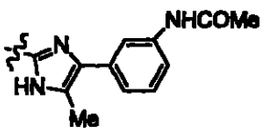
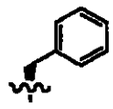
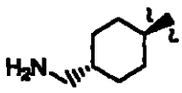
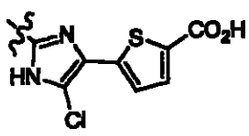
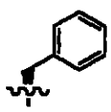
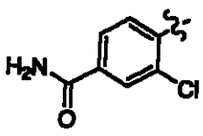
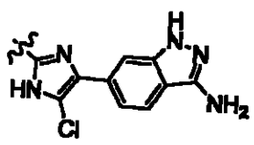
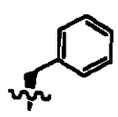
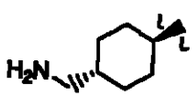
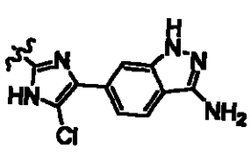
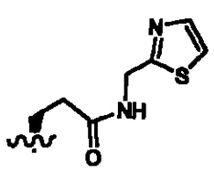
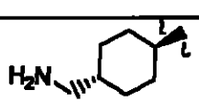
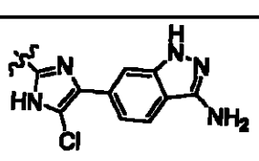
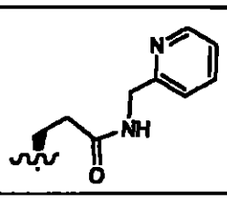
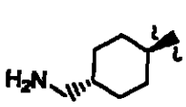
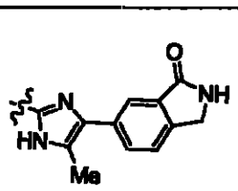
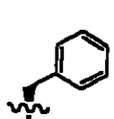
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
287				.627.4
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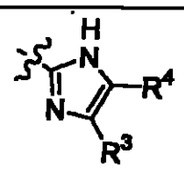
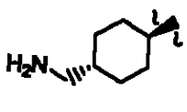
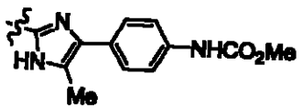
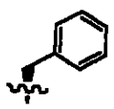
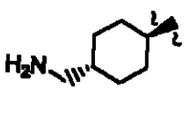
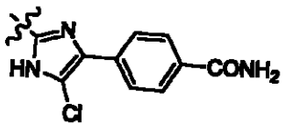
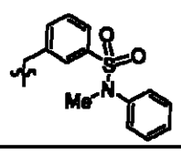
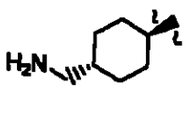
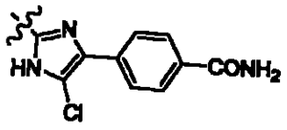
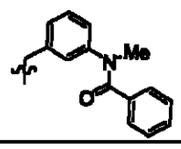
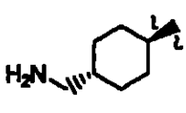
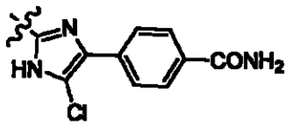
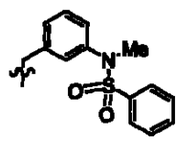
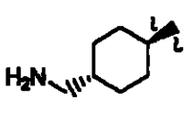
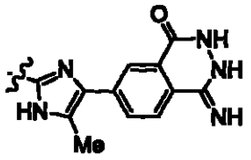
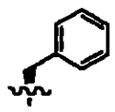
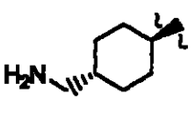
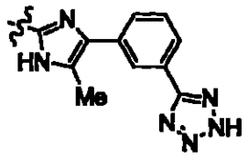
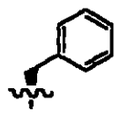
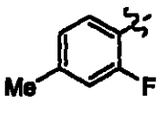
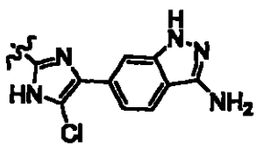
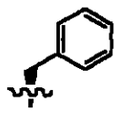
(627) 630

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
293				661.4
294				510.3
295				
296				
297				474.3
298				433.3
299				642.5

# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
300				625.4
301				625.4
302				641.4
303				653.5
304				457.3
305				545.3

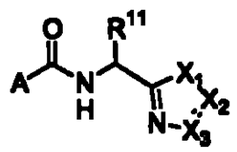
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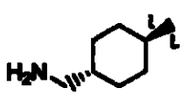
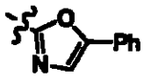
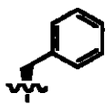
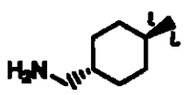
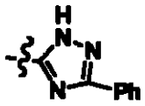
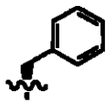
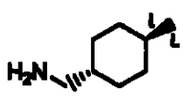
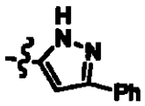
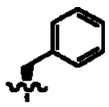
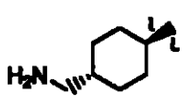
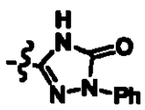
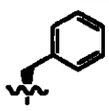
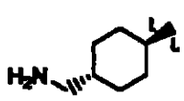
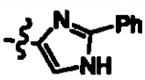
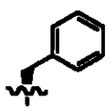
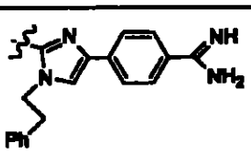
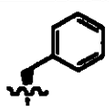
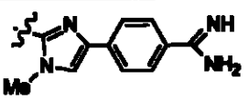
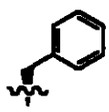
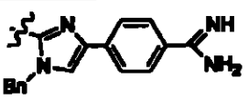
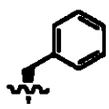
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
306				510.3
307				474.4
308				487.2
309				534.3
310				558.3
311				552.3
312				472.3

# Ej.	A		R^{11}	Espectro de masas (m/z) $(M+H)^+$
313				490.3
314				649.2
315				613.3
316				649.2
317				500.3
318				485.3
319				489.3

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Tabla 2



# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
48				404.3
49				404.2
50				403.1
51				420.1
52				403.3
125				514.3
126				424.2
127				500.2

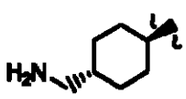
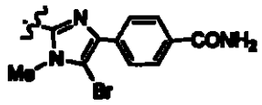
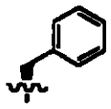
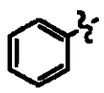
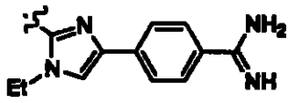
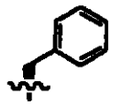
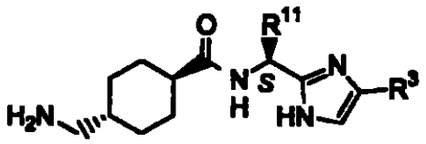
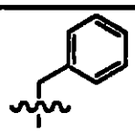
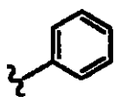
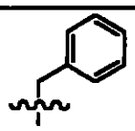
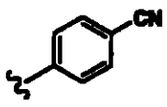
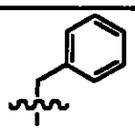
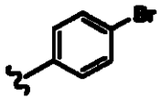
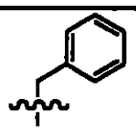
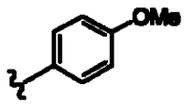
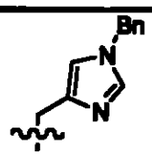
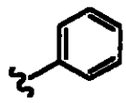
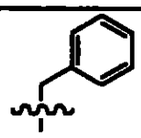
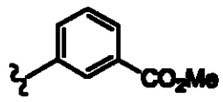
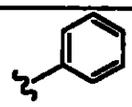
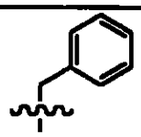
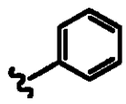
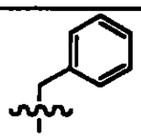
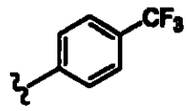
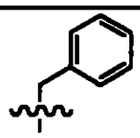
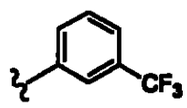
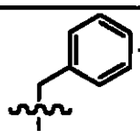
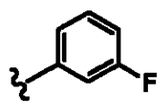
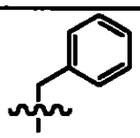
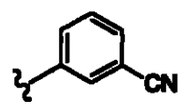
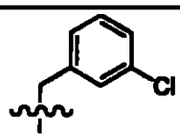
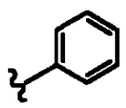
# Ej	A		R^{11}	Espectro de masa (m/z) $(M+H)^+$
139				538.2 540.2
182				450.2

Tabla 3



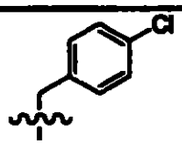
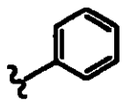
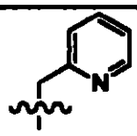
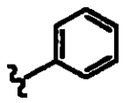
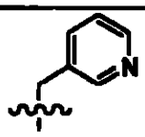
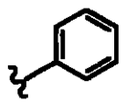
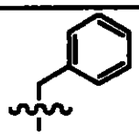
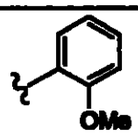
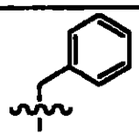
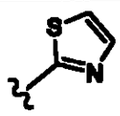
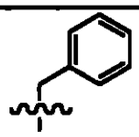
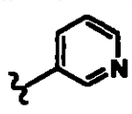
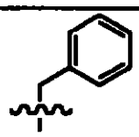
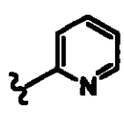
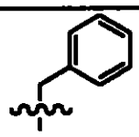
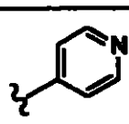
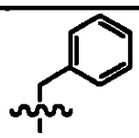
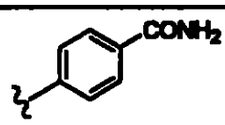
El	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
2			403.2
3			428.15
4			481.09
5			433.25

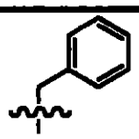
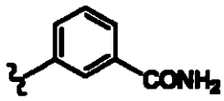
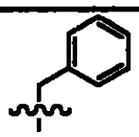
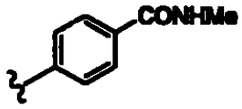
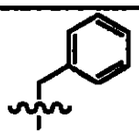
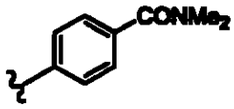
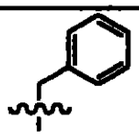
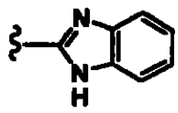
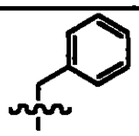
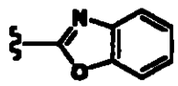
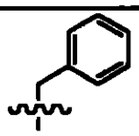
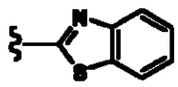
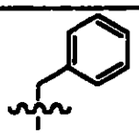
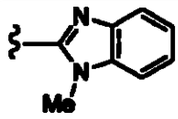
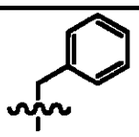
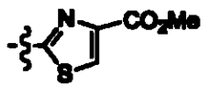
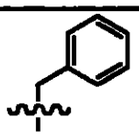
635
636

Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
6			483.23
7			461.25
8	Me		327.21
9			417.27
10			471.24
11			471.24
12			421.24
13			428.30
16			437.21

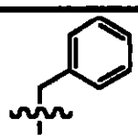
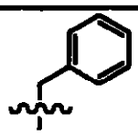
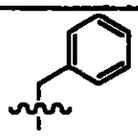
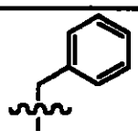
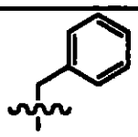
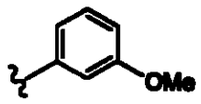
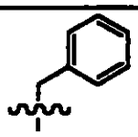
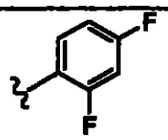
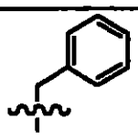
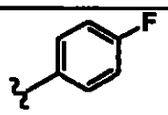
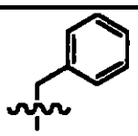
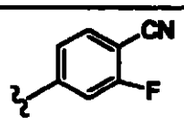
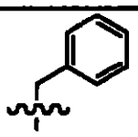
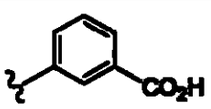
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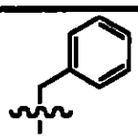
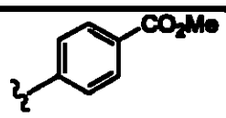
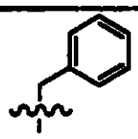
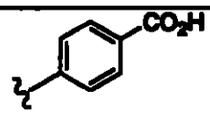
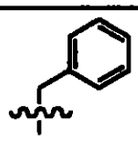
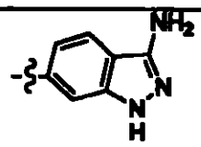
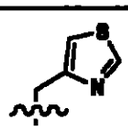
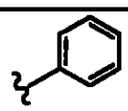
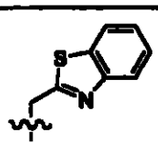
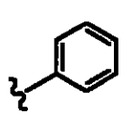
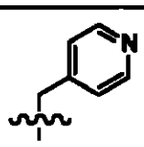
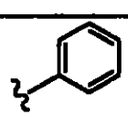
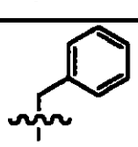
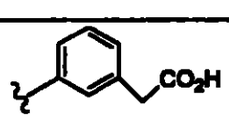
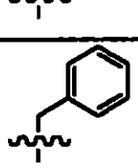
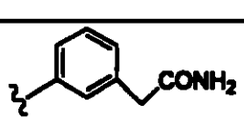
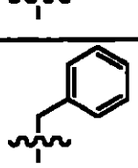
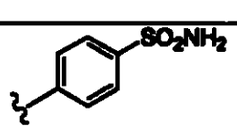
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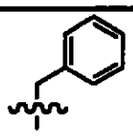
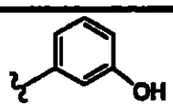
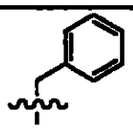
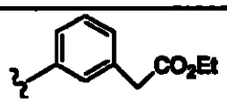
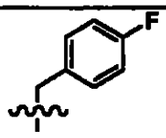
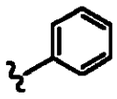
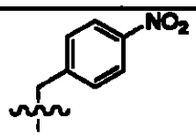
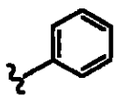
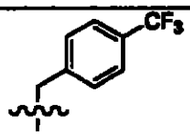
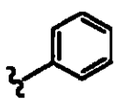
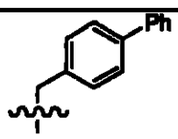
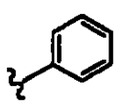
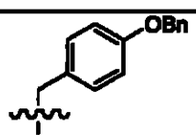
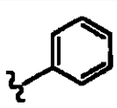
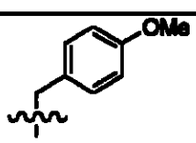
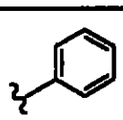
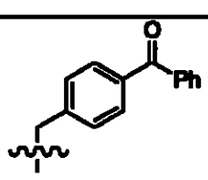
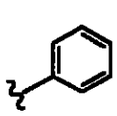
Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
17			437.21
18			404.25
19			404.25
20			433.26
21			432.18
22			404.25
23			404.25
24			404.25
28			446.26

Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
29			446.2
30			460.27
31			474.29
32			443.25
33			444.24
34			460.22
35			457.27
36			468.21
37		$-CO_2Me$	385.33

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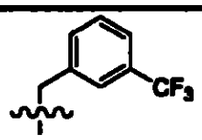
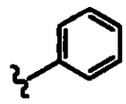
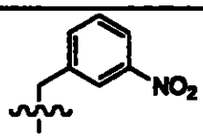
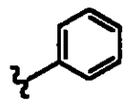
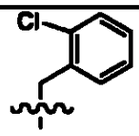
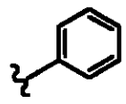
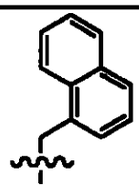
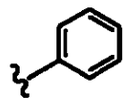
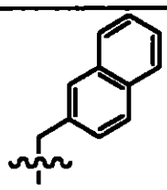
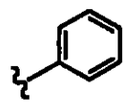
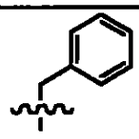
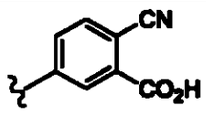
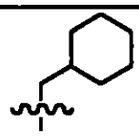
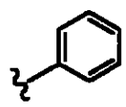
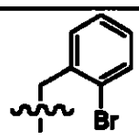
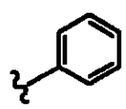
Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
38		$-CO_2H$	371.21
39		$-CONHCH_2CO_2Et$	478.24
40		$-CONHCH_2CO_2H$	428.22
41		-CONHBn	460.27
62			433.22
63			439.23
64			421.24
65			446.23
66			447.24

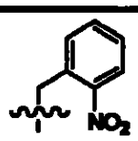
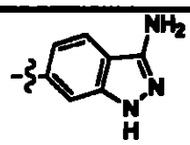
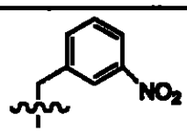
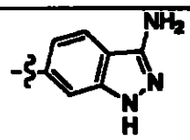
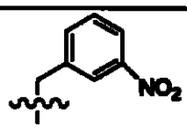
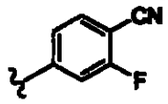
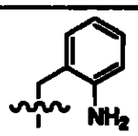
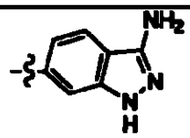
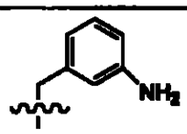
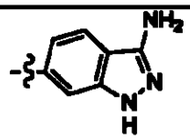
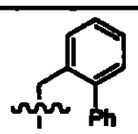
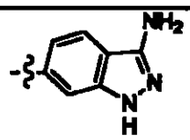
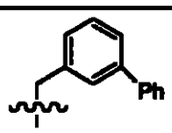
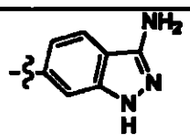
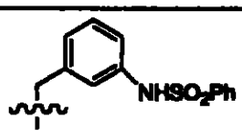
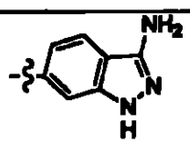
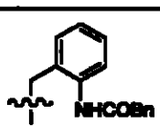
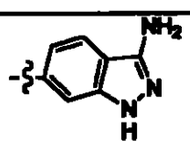
Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
67			461.26
68			447.24
69			458.27
79			410.2
80			460.1
81			404.0
87			461.1
88			460.2
89			482.1

Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
90			419.2
91			489.2
94			421.3
95			448.2
96			471.3
97			479.3
98			509.3
99			433.3
100			507.5

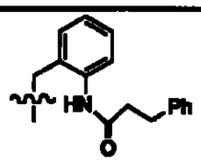
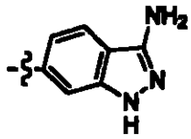
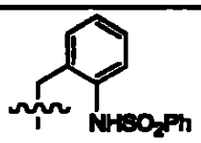
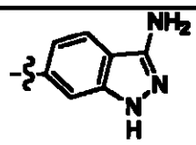
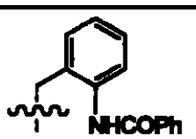
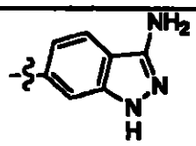
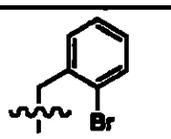
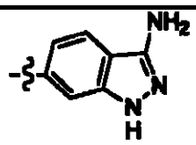
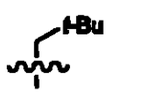
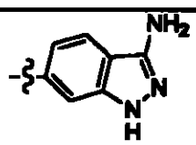
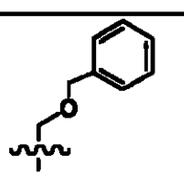
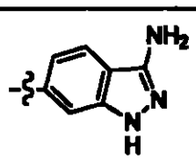
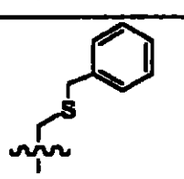
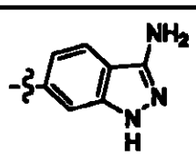
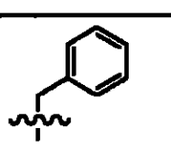
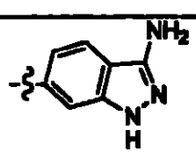
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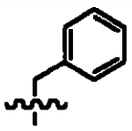
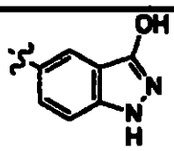
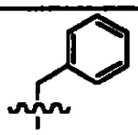
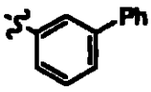
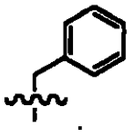
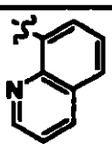
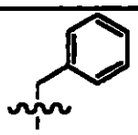
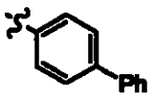
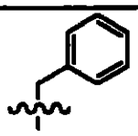
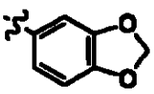
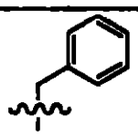
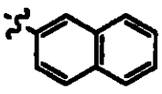
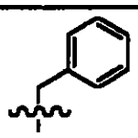
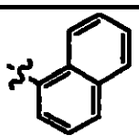
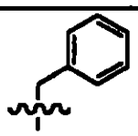
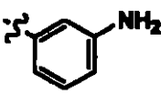
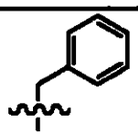
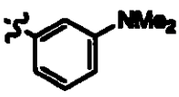
642

Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
101			471.4
102			448.2
103			437.4
104			453.5
105			453.4
109			472.3
110			409.4
111			481.3

Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
148			503.2
149			503.1
150			491.0
151			473.3
152			473.2
153			534.3
154			534.3
156			613.1
159			591.3

644

Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
163			605.3
164			613.2
166			577.3
167			537.9
168			438.1
169			488.1
170			504.1
201			457.9

Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
202			459.2
207			479.3
208			454.3
209			479.3
210			447.3
211			453.2
212			453.3
216			418.3
234			446.3

646

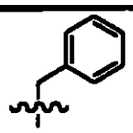
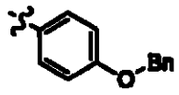
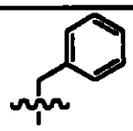
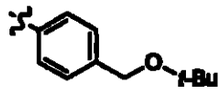
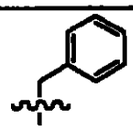
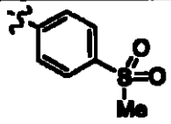
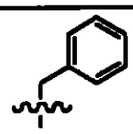
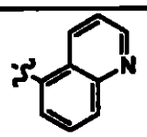
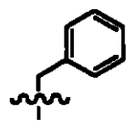
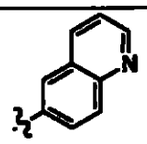
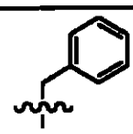
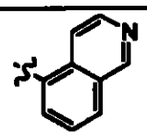
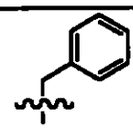
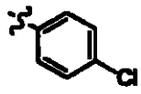
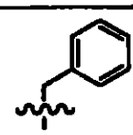
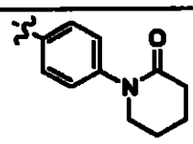
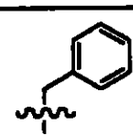
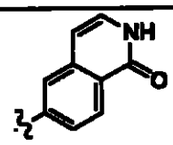
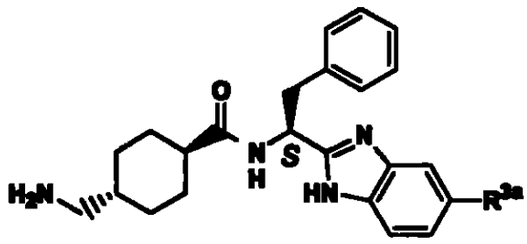
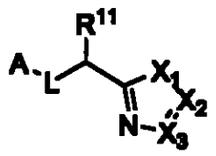
Ej	R^{11}	R^3	Espectro de masa (m/z), $(M+H)^+$
236			509.3
237			489.3
240			481.2
245			454.3
246			454.3
247			454.3
258			437.3
259			500.3
260			470.3

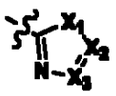
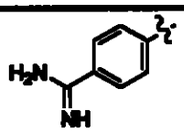
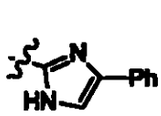
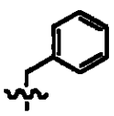
Tabla 4



# Ej	R^{3a}	Espectro de masa (m/z) $(M+H)^+$
42	CO_2Et	435.3
43	CO_2H	421.2
44	$CONH_2$	420.2
45	$-CH_2CO_2Et$	463.4
46	$-CH_2CO_2H$	435.4
47	$-CH_2CONH_2$	434.3

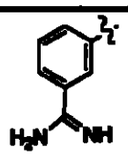
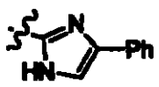
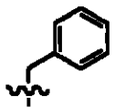
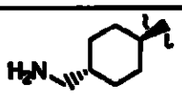
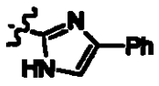
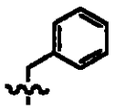
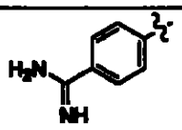
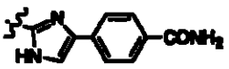
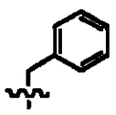
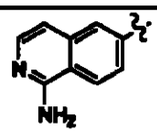
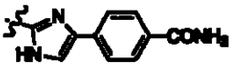
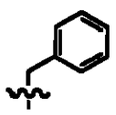
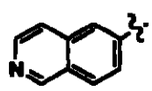
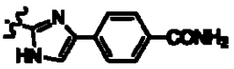
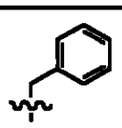
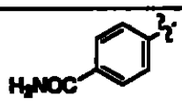
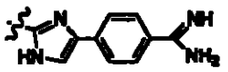
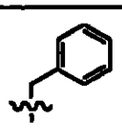
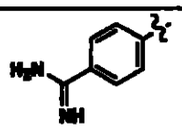
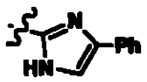
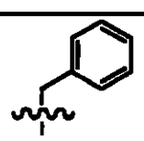
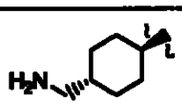
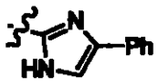
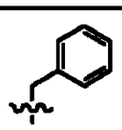
Tabla 5



# Ej	A	L		R^{11}	Espectro de masa (m/z) $(M+H)^+$
53		-NHCO-			410.20

647

648

# Ej	A	L		R^{11}	Espectro de masa (m/z) $(M+H)^+$
54		-NHCO-			410.20
55		-NHCO-			410.20
56		-NHCO-			453.20
57		-NHCO-			477.3
58		-NHCO-			462.19
59		-NHCO-			453.4
61		$-NHCOCH_2-$			424.21
77		NHCONH			418.1

649

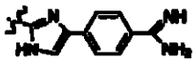
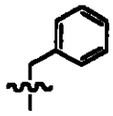
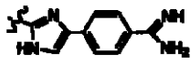
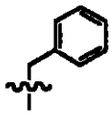
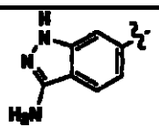
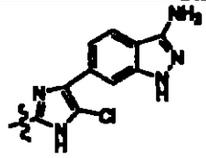
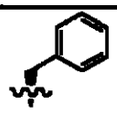
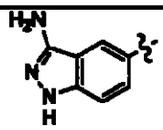
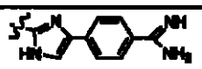
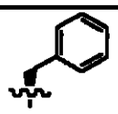
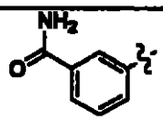
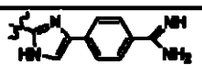
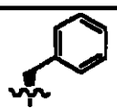
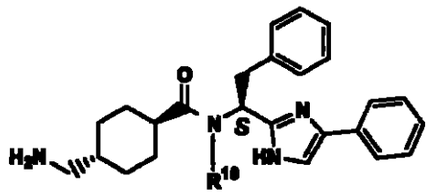
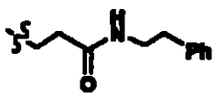
# Ej	A	L		R^{11}	Espectro de masa (m/z) $(M+H)^+$
92		-NHCO-			453.2
93		-NHCO-			410.2
138		$-CH_2CONH-$			526.3
184		$-SO_2NH-$			501.5
185		$-SO_2NH-$			489.0

Tabla 6

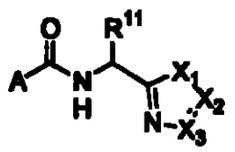


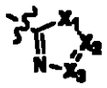
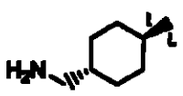
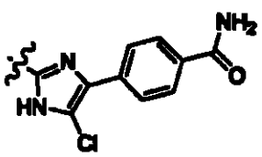
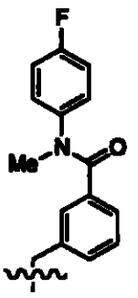
# Ej	R^{10}	Espectro de masa (m/z) $(M+H)^+$
70	Bn	493.20

# Ej	R^{10}	Espectro de masa (m/z) $(M+H)^+$
71	$-CH_2CH_2Ph$	507.31
72	$-CH_2CH_2CO_2Et$	489.62
74	$-CH_2CH_2CONH_2$	474.62
85		578.4

Usando combinaciones de las rutas sintéticas arriba descritas y los procedimientos experimentales junto con métodos conocidos por alguien de experiencia en el arte de la síntesis orgánica, los compuestos adicionales de esta invención mostrados a continuación en la Tabla 6, pueden prepararse.

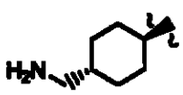
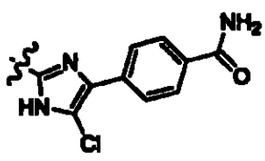
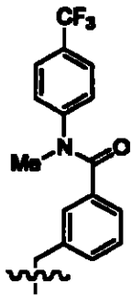
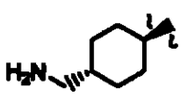
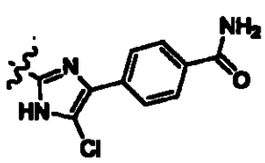
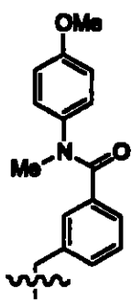
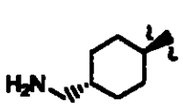
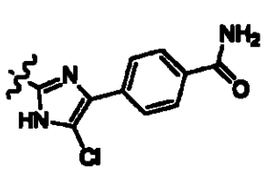
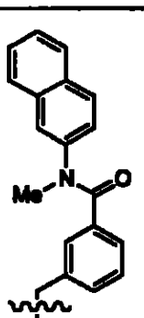
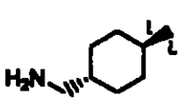
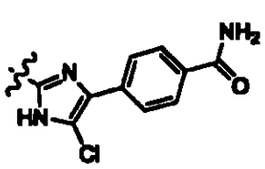
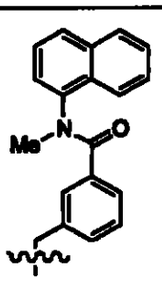
Tabla 7



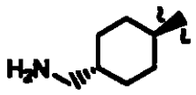
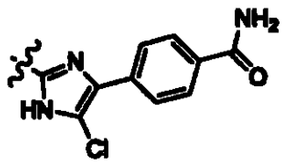
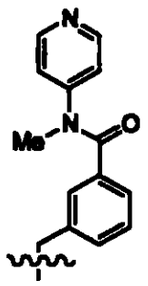
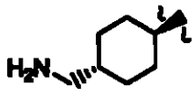
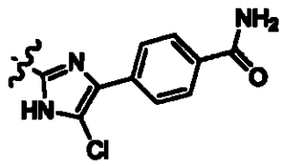
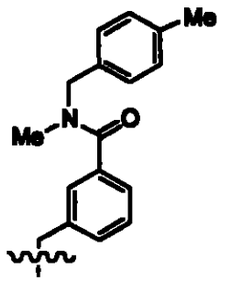
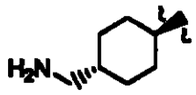
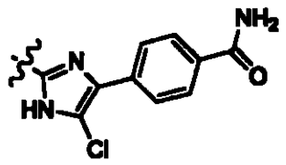
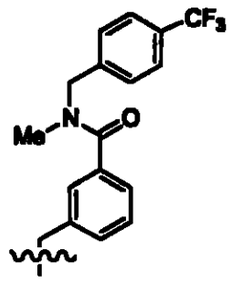
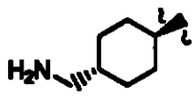
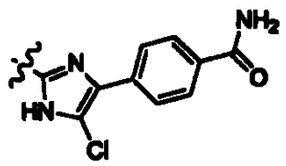
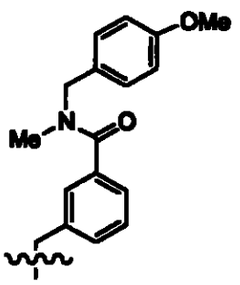
# Ej	A		R^{11}
1001			

646

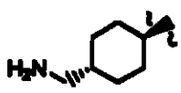
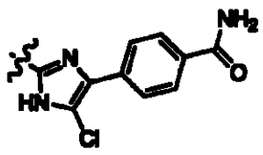
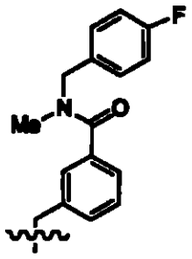
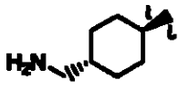
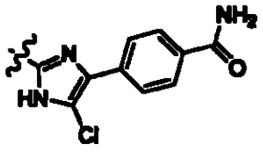
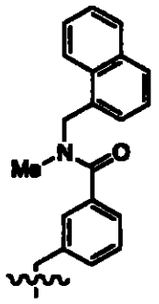
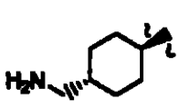
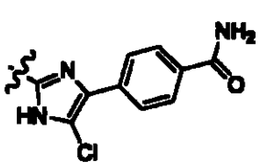
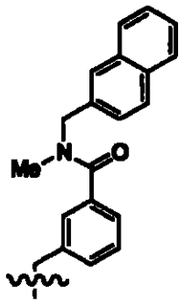
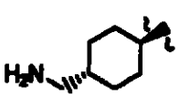
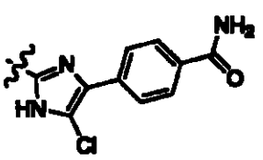
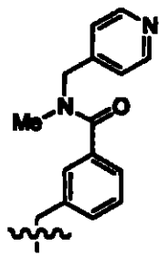
651

# Ej	A		R^{11}
1002			
1003			
1004			
1005			

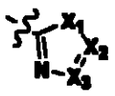
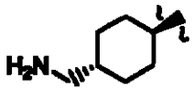
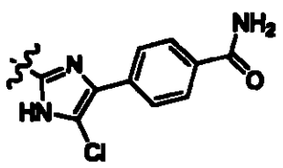
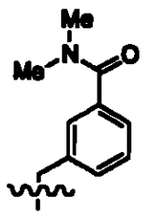
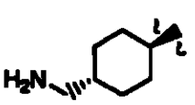
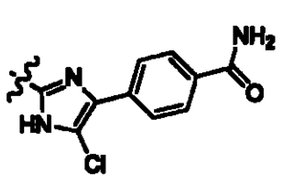
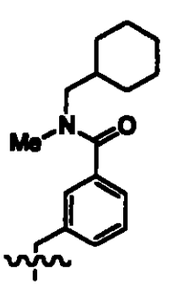
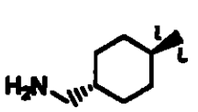
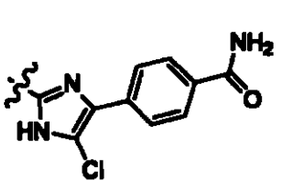
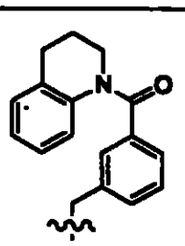
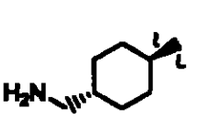
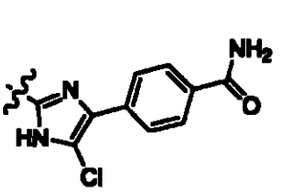
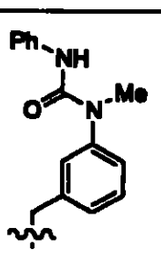
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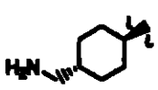
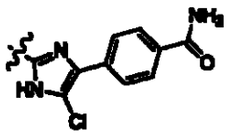
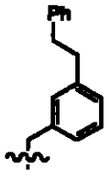
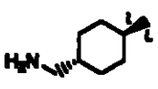
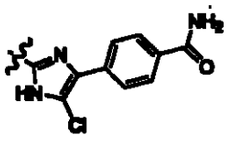
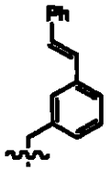
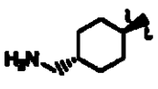
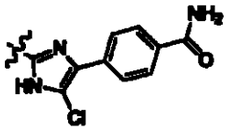
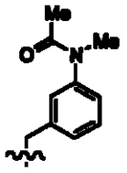
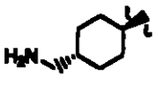
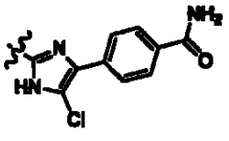
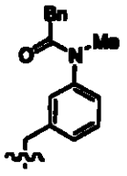
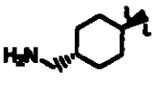
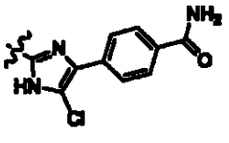
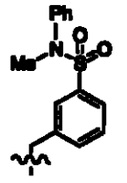
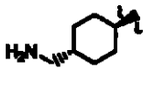
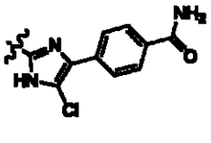
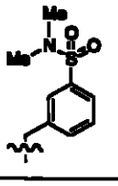
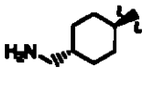
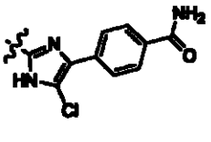
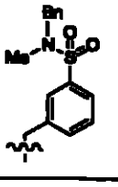
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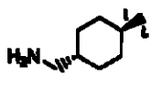
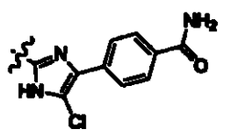
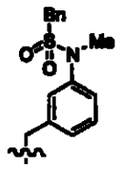
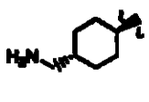
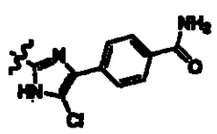
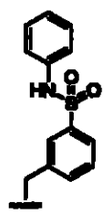
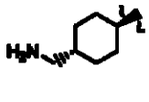
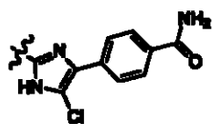
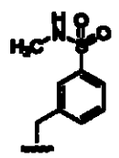
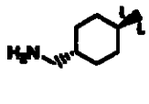
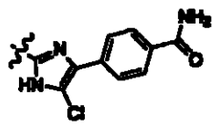
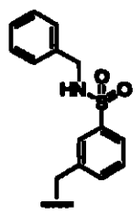
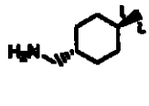
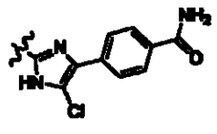
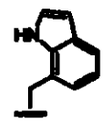
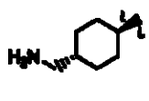
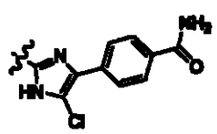
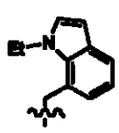
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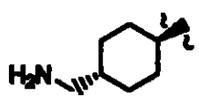
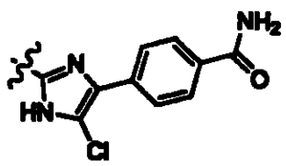
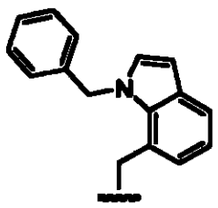
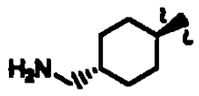
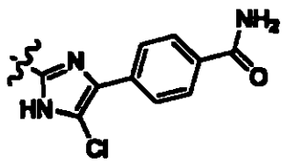
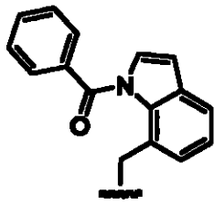
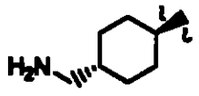
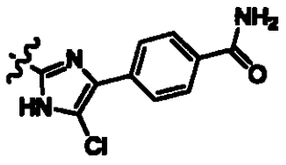
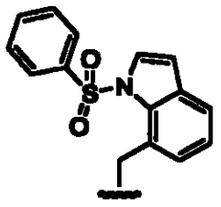
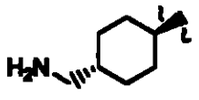
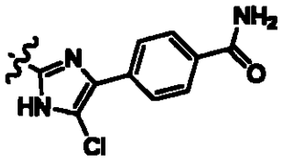
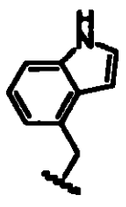
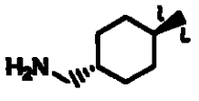
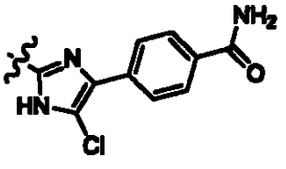
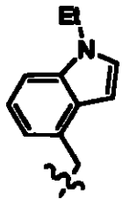
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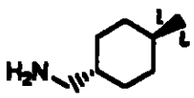
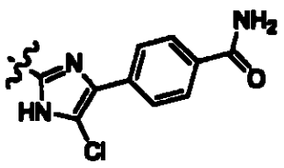
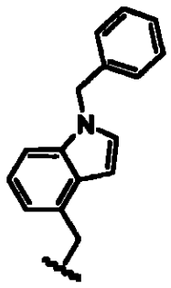
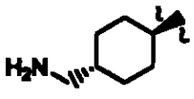
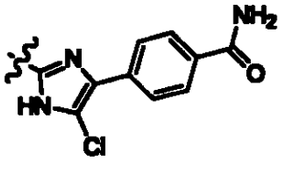
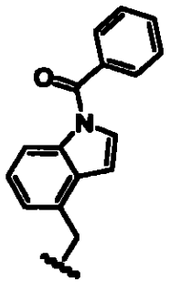
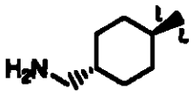
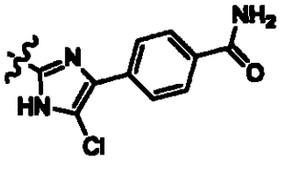
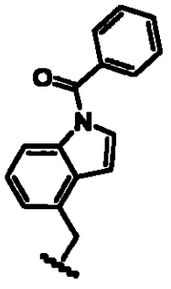
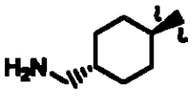
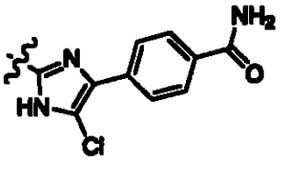
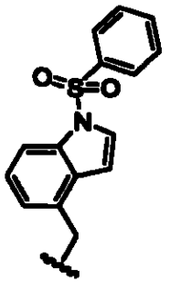
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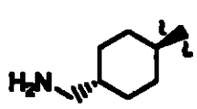
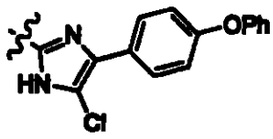
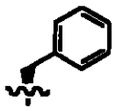
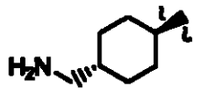
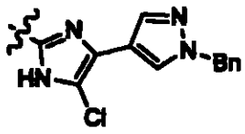
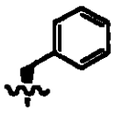
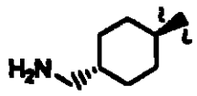
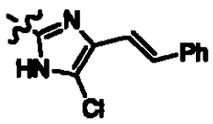
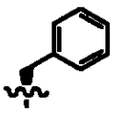
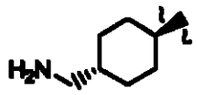
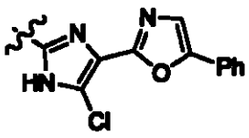
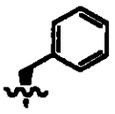
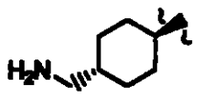
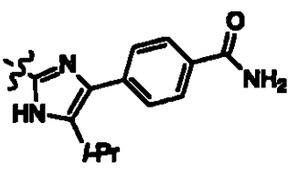
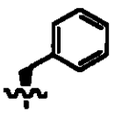
实施	A		R^{11}
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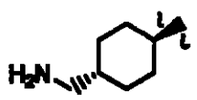
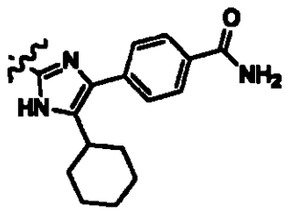
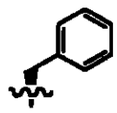
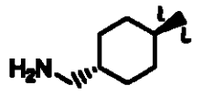
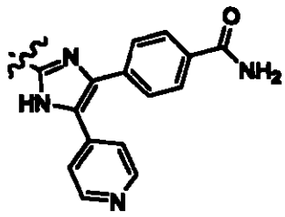
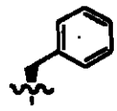
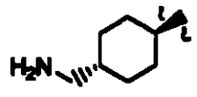
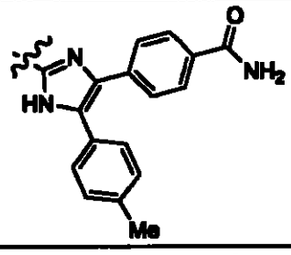
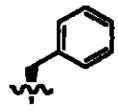
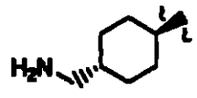
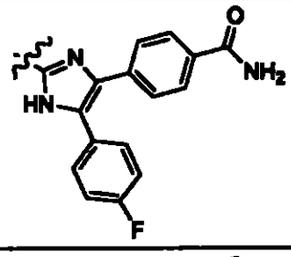
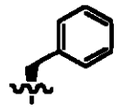
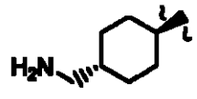
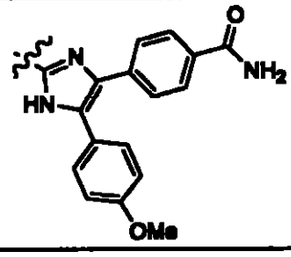
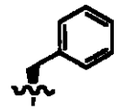
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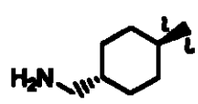
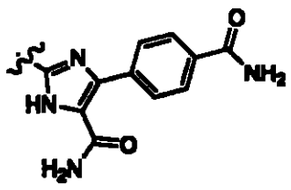
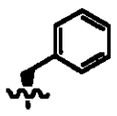
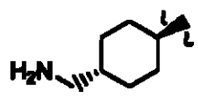
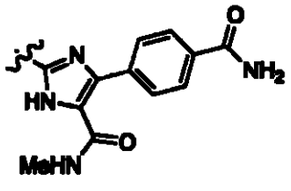
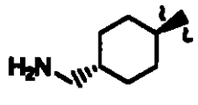
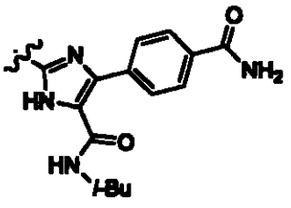
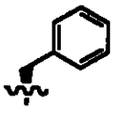
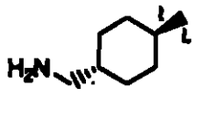
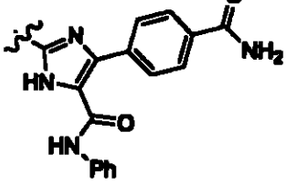
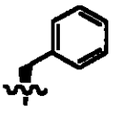
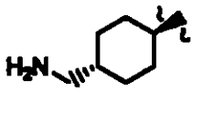
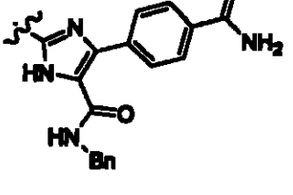
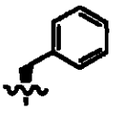
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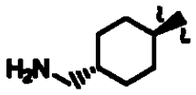
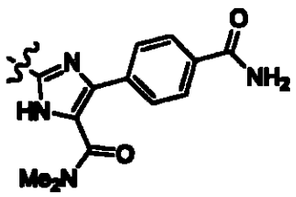
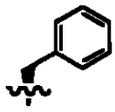
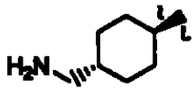
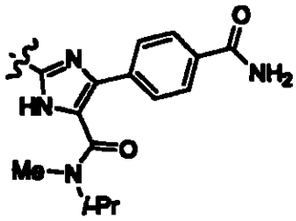
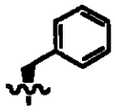
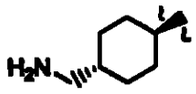
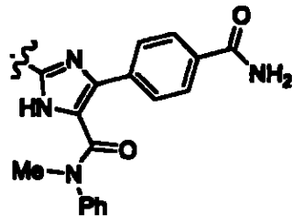
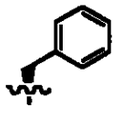
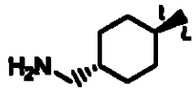
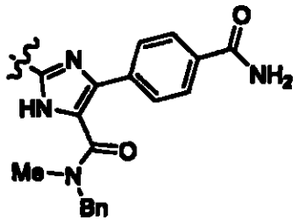
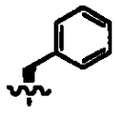
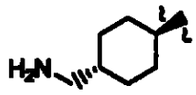
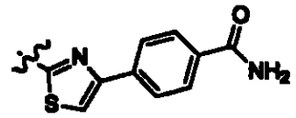
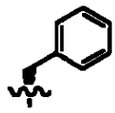
659

# Ej	A		R^{11}
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1044			
1045			
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1047			

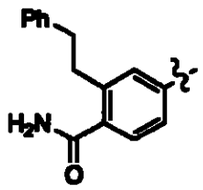
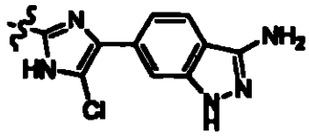
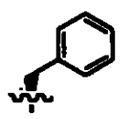
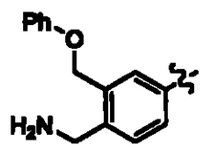
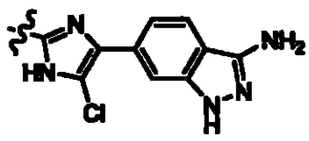
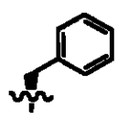
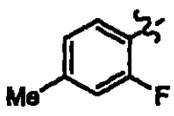
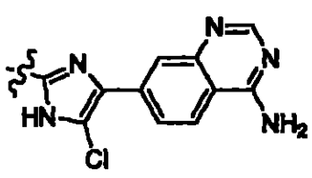
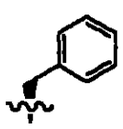
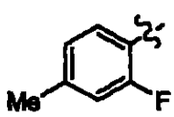
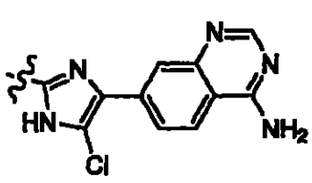
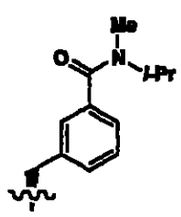
# Ej	A		R^{11}
1048			
1049			
1050			
1051			
1052			

# Ej	A		R^{11}
1053			
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1057			

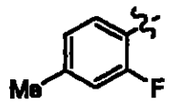
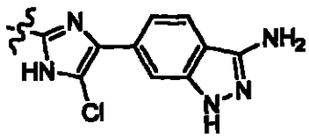
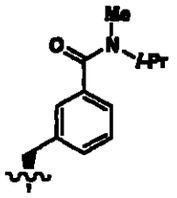
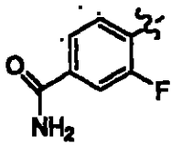
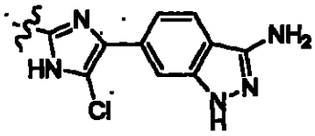
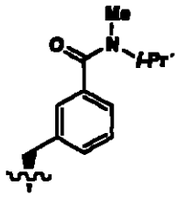
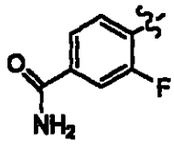
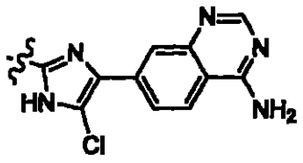
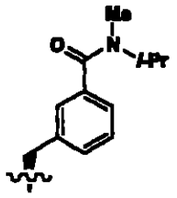
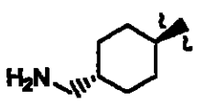
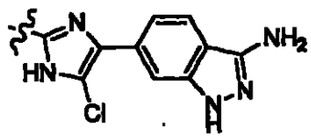
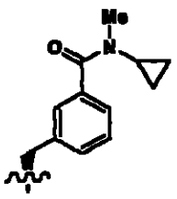
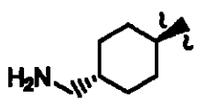
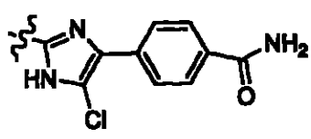
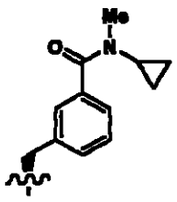
662

# Ej	A		R^{11}
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1059			
1060			
1061			
1062			

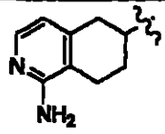
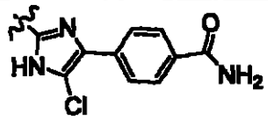
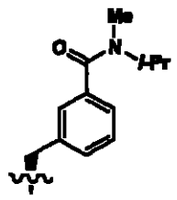
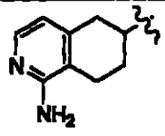
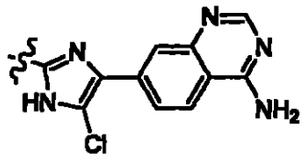
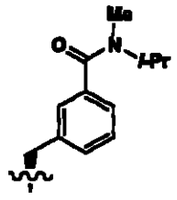
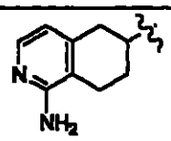
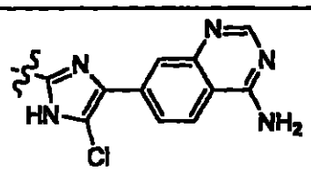
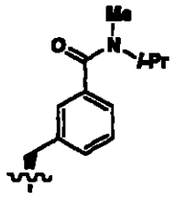
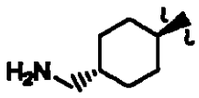
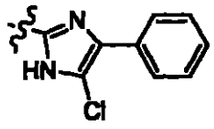
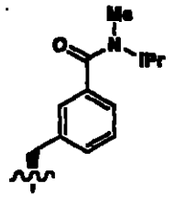
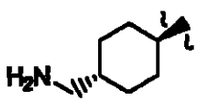
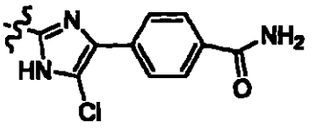
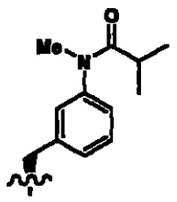
663

# Ej	A		R^{11}
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1064			
1065			
1066			

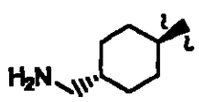
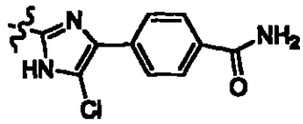
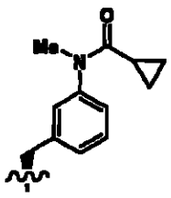
664

# Ej.	A		R^{II}
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1068			
1069			
1070			
1071			

660
665

# Ej.	A		R^{11}
1072			
1073			
1074			
1075			
1076			

666

# Ej.	A		R^{11}
1077			

Utilidad

Los compuestos de esta invención son inhibidores del factor XIa y son útiles como anticoagulantes para el tratamiento o prevención de trastornos tromboembólicos en mamíferos (esto es, trastornos asociados con el factor de XIa). En general, un trastorno tromboembólico es una enfermedad circulatoria causada por coágulos sanguíneos (esto es, enfermedades que involucran la formación de fibrina, activación de plaquetas, y/o agregación de plaquetas). El termino "trastornos tromboembólicos" como se usa en la presente incluye trastornos tromboembólicos cardiovasculares arteriales, trastornos tromboembólicos cardiovasculares o cerebrovasculares venosos, y trastornos tromboembólicos en las cavidades del corazón. El término "trastornos tromboembólicos" como se usa en la presente también incluye trastornos específicos seleccionados de, pero no limitados a, angina inestable u otros síndromes coronarios agudos,

fibrilación arterial, primer infarto al miocardio o recurrente, muerte súbita isquémica, ataque isquémico transitorio, apoplejía, ateroesclerosis, enfermedad arterial oclusiva periférica, trombosis venosa, trombosis de vena profunda, tromboflebitis, embolia arterial, trombosis arterial coronaria, trombosis arteria cerebral, embolia cerebral, embolia de riñón, embolia pulmonar, y trombosis que resulta de (a) válvulas prostéticas, u otros implantes, (b) catéteres de introducción, (c) endoprótesis vasculares, (d) derivación cardiopulmonar (e) hemodiálisis, o (f) otros procedimientos en los cuales la sangre se expone a una superficie artificial que promueve la trombosis. Se notará que la trombosis incluye la oclusión (por ejemplo, después de una derivación) y reoclusión (por ejemplo, durante o después de una angioplastia coronaria transluminar percutánea). Los trastornos tromboembólicos pueden resultar de condiciones que incluyen, pero no se limitan a ateroesclerosis, complicaciones quirúrgicas o de cirugía, inmovilización prolongada, fibrilación arterial, trombofilia congénita, cáncer, diabetes, efectos de medicamentos u hormonas, y complicaciones de embarazo. El efecto anticoagulante de los compuestos de la presente invención se considera que se debe a la inhibición de serina proteasas que están involucradas en la cascada de coagulación y/o el sistema de activación por contacto, más específicamente, la inhibición de los factores

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de coagulación: factor XIa, factor VIIa, factor IXa, factor Xa, calicreína en el plasma o trombina.

Los compuestos de esta invención también son inhibidores de la calicreína en el plasma y son útiles como agentes inflamatorios para el tratamiento o prevención de enfermedades asociadas con una activación del sistema de activación por contacto (por ejemplo, trastornos asociados con la calicreína en el plasma). En general, un trastorno del sistema de activación por contacto es una enfermedad causada por la activación de la sangre en superficies artificiales, incluyendo válvulas prostéticas u otros implantes, catéteres de introducción, endoprótesis vasculares, derivación cardiopulmonar, hemodiálisis, microorganismos (por ejemplo, virus, bacterias) u otros procedimientos en los cuales la sangre se expone a una superficie artificial que promueve la activación por contacto, coágulos sanguíneos (esto es, enfermedades que involucran la formación de fibrina, activación de plaquetas, y/o agregación de plaquetas). También se incluye el síndrome de respuesta inflamatorio sistémico, sepsis, síndrome de distensión respiratorio agudo, angioedema hereditario u otras deficiencias heredadas o adquiridas de los componentes de activación por contacto o sus inhibidores (calicreína de plasma, factor XIIa, cininógeno de alto peso molecular, inhibidor de C1 esterasa). También puede incluir inflamaciones agudas y crónicas de

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articulaciones, vasos u otros órganos de mamíferos.

La efectividad de los compuestos de la presente invención como inhibidores de los factores de coagulación XIa, VIIa, IXa, Xa, calicreína de plasma o trombina puede determinarse usando una proteasa purificada relevante respectivamente, y un substrato sintético apropiado. La relación de hidrólisis del substrato cromogénico o fluorogénico por la serina proteasa relevante se mide tanto en ausencia como en presencia de los compuestos de la presente invención. La hidrólisis del substrato resultó en la liberación de pNA (para nitroanilina), que se monitorea espectrofotométricamente al medir el incremento en absorbancia a 405 nm, o la liberación de AMC (amino metilcumarina que se monitorea espectrofotométricamente al medir el incremento en la emisión a 460 nm con excitación a 380 nm. Una reducción en la relación de absorbancia o cambio de fluorescencia en la presencia del inhibidor indica la inhibición de la enzima. Tales métodos son conocidos por aquellos expertos en la técnica. Los resultados de este ensayo se expresan como la constante inhibidora, K_i.

Se hacen las determinaciones del factor XIa en solución amortiguadora HEPES 50 mM a pH 7.4 que contiene NaCl 145 mM, KCl 5mM, y PEG 8000 al 0.1% (polietilen glicol; JT Baker o Fisher Scientific). Se hacen las determinaciones usando Factor XIa humano purificado a una concentración final

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de 75-200 pM (Haematologic Technologies) y el substrato sintético S-2366 (pyroGlu-Pro-Arg-pNA; Chromagenix) a una concentración de 0.0002-0.00025 M. En general, los compuestos preferidos de la presente invención, tales como los compuestos particulares descritos en los ejemplos anteriores, se han identificado para hacer activos y exhibir K_i de igual a menos que 15 μM en el ensayo del factor XIa, por lo que demuestran en la utilidad de los compuestos de la presente invención como inhibidores específicamente efectivos de la coagulación del factor XIa. Los compuestos más preferidos tienen K_i de igual o menos que 5 μM, preferiblemente igual o menos que 1 μM más preferiblemente igual a o menor a 0.5μM.

Se hacen determinaciones del factor VIIa en cloruro de calcio 0.005 M, cloruro de sodio 0.15 M, solución amortiguadora HEPES 0.05 M que contiene PEG 8000 al 0.5% a un pH de 7.4. Se hacen las determinaciones usando el factor VIIa humano purificado (Haematologic Technologies) o factor VIIa humano recombinante (Novo Nordisk) a una concentración de ensayo final de 2-5 nM, factor de tejido recombinante soluble a una concentración de 18-35 nM, y el substrato sintético H-D-Ile-Pro-Arg-pNA (S-2288; Chromogenix o BMPM-2; AnaSpec) a una concentración de 0.001 M. En general, los compuestos probados en el ensayo del factor VIIa se considera que son activos si perciben un K_i de igual a o menos a 15 μM.

Las determinaciones del factor IXa se hacen en

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cloruro de calcio 0.005 M, cloruro de sodio 0.1 M, base TRIS 0.05 M y PEG 8000 a 0.5% a un pH de 7.4. Se hacen las determinaciones usando el factor IXa humano purificado (Haematologic Technologies) a una concentración de ensayo final de 20-100 nM y el substrato sintético PCIXA2100-B (CenterChem) o Pefafluor IXa 3688 (H-D-Leu-Ph'Gly-Arg-AMC; CenterChem) a una concentración de 0.0004-0.0005 M. En general los compuestos probados en el ensayo de factor IXa se considera que son activos si exhibe un K_i de igual a o menos a 15 μM.

Las determinaciones del factor Xa se hacen en solución amortiguadora de fosfato de sodio 0.1 M a un pH de 7.4 que contiene cloruro de sodio 0.2 M y PEG 8000 al 0.5%. Se hacen las determinaciones usando el factor Xa humano purificado (Haematologic Technologies) a una concentración de ensayo final de 150-1000 pM y el substrato sintético S-2222 (Bz-Ile-Glu(gamma-OMe, 50%)-Gly-Arg-pNA; Chromagenix), a una concentración de 0.0002-0.0003 M. En general los compuestos probados en el ensayo de factor Xa se considera que son activos si exhiben un K_i de igual a o menos a 15 μM.

Las determinaciones de calicreína de plasma se hicieron en solución amortiguadora de fosfato de sodio 0.1 M a un pH de 7.4 que contiene cloruro de sodio 0.2 M y PEG 8000 al 0,5%. Se hacen determinaciones usando calicreína humana purificada (Enzyme Research Laboratories) a un ensayo de

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concentración final de 200 pM y el substrato sintético S-2302 (H-(D)-Pro-Phe-Arg-pNA; Chromagenix) a una concentración de 0.00008-0.0004 M. El valor Km usado para el cálculo de Ki fue 0.00005 hasta 0.00007 M. En general, los compuestos probados en el ensayo de calicreína en el plasma se considera que son activos si exhiben un K_i de igual a o menos a 15 μM.

Las determinaciones de trombina se hacen en solución amortiguadora de fosfato de sodio 0.1 M en un pH de 7.4 que contiene cloruro de sodio 0.2 M y PEG 8000 al 0.5%. Se hacen las determinaciones usando la alfa trombina humana purificada (Haematologic Technologies o Enzyme Research Laboratories) a una concentración de ensayo final de 200-250 pM y un substrato sintético S-2366 (pyroGlu-Pro-Arg-pNA; Chromogenix) a una concentración de 0.0002 M. En general, los compuestos probados en el ensayo de trombina se considera que son activos si exhiben un K_i de igual a o menos a 15 μM.

En general, los compuestos preferidos de la presente invención han demostrado valores K_i de igual o menos a 15 μM en al menos uno de los ensayos anteriores, por lo que confirma la utilidad de los compuestos de la presente invención como inhibidores efectivos de la cascada de coagulación y/o el sistema de activación por contacto, y útiles como anticoagulantes para la prevención o tratamiento de trastornos tromboembólicos en mamíferos y/o como agentes anti-inflamatorios para la prevención de tratamiento de

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trastornos inflamatorios en mamíferos.

La constante de Michaelis, K_m, para la hidrólisis del sustratopara cada proteasa, se determinó a 25°C usando el método de Lineweaver y Burk. Se determinaron los valores K_i al permitir que la proteasa reaccionara con el sustrato en presencia del inhibidor. Se permitió que las reacciones fueran por periodos de 20-180 minutos (dependiendo en la proteasa) y las velocidades (relación del cambio de la absorbancia o fluorescencia contra tiempo). Se usó la siguiente relación para calcular los valores K_i:

$(V_o-V_s)/V_s= I/(K_i (1 + S/K_m))$ para un inhibidor competitivo con un sitio de enlace; o

$V_s/V_o = A + ((B-A)/1 + ((IC_{50}/(I)^n)))$ y

$K_i = IC_{50}/(1+ S/K_m)$ por un inhibidor competitivo

donde:

V_o es la velocidad del control en ausencia del inhibidor;

V_s es la velocidad en presencia del inhibidor;

I es la concentración del inhibidor;

A es la actividad mínima restante (usualmente cerrada a cero);

B es la actividad máxima restante (usualmente cerrada a 1.0);

n es el coeficiente de Hill, una medida del número y cooperación de los sitios de enlace inhibidores

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potenciales;

IC_{50} es la concentración del inhibidor que produce una inhibición del 50% bajo las condiciones de ensayo;

K_i es la constante de disociación del complejo enzima:inhibidor;

S es la concentración del substrato; y

K_m es la constante de Michaelis por el substrato.

La efectividad de los compuestos de la presente invención como inhibidores de la coagulación de los factores XIa, VIIa, IXa, Xa, o trombina, puede determinarse usando los modelos de trombosis relevantes in vivo, incluyendo los modelos de trombosis arterial carótida inducida eléctricamente In vivo y los modelos de trombosis de desviación arterio-venosa en conejo In vivo.

Modelo de Trombosis Arterial Carótida Inducida Eléctricamente in vivo:

El efecto antitrombótico de los compuestos de la presente invención puede demostrarse en el modelo de trombosis arterial carótida inducida eléctricamente (ECAT) en conejo. En este modelo los conejos se anestesian con una mezcla de cetamina (50 mg/kg i.m.) y xilazina (10 mg/kg i.m.). La vena femoral y la arteria femoral se aíslan y cateterizan. La arteria carótida también se aísla de tal manera que el flujo sanguíneo pueda medirse con una sonda de

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flujo calibrado que se enlaza a un flujómetro. Se coloca un electrodo de gancho bipolar de acero inoxidable en la arteria carótida y se coloca caudalmente con relación a la sonda de flujo como medio para aplicar estímulos eléctricos. Con objeto de proteger el tejido circundante, se coloca una pieza de Parafilm bajo el electrodo.

Los compuestos de prueba se considera que son efectivos como anticoagulantes con base en su capacidad para mantener el flujo sanguíneo en la arteria carótida después de la inducción de trombosis por un estimulo eléctrico. El compuesto de prueba o vehículo se da como una infusión intravenosa continua por medio de la vena femoral iniciando una hora antes de la estimulación eléctrica y continuando hasta el final de la prueba. La trombosis se induce al aplicar una corriente eléctrica directa de 4 mA durante 3 minutos a la superficie arterial externa usando una unidad de corriente constante y un estimulador d.c. El flujo sanguíneo carótido se monitorea y se observa el tiempo para obstruir (reducción del flujo sanguíneo hasta cero después de la inducción de trombosis) en minutos. El cambio en el flujo sanguíneo observado se calcula como el porcentaje de flujo sanguíneo antes de la inducción de trombosis y proporciona una medida del efecto del compuesto de prueba cuando se compara con el caso en donde se administran compuestos. Esta información se usa para estimar el valor ED_{50}, la dosis que

incrementa el flujo sanguíneo hasta el 50% del control (flujo sanguíneo antes de la inducción de trombosis) y se realiza por una regresión de mínimos cuadrados no lineal.

Modelo De Trombosis de Desviación Venosa Arterial en Conejos in Vivo

El efecto antitrombótico de los compuestos de la presente invención, se puede demostrar en un modelo de trombosis desviado arterio-venoso de conejo (AV). En este modelo, se usaron conejos que pesaban 2-3 kg anestesiados con una mezcla de xilazina (10 mg/ kg i.m) y cetamina (50 mg/kg i.m.). Se conectó un dispositivo de desviación AV llenado con solución salina entre la cánula de la arteria femoral y la vena femoral. El dispositivo de desviación AV consiste de una pieza y tubería de tygon de 6 cm que contiene una pieza de hilo de seda. La sangre fluirá de la arteria femoral por medio de la desviación AV dentro de la vena femoral. La exposición del flujo de sangre al hilo de seda inducirá la formación de un trombo importante. Después de cuarenta minutos, se desconecta la desviación y se pesa el hilo de seda cubierto con el trombo. Los agentes de prueba o vehículos se darán (i.v., i.p. s.c., u oralmente) previo a la abertura de la derivación AV. El porcentaje de inhibición de la formación del trombo se determina para cada grupo de tratamiento. Los valores ID_{50} (dosis que produce un 50% de

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inhibición de la formación del trombo) se estiman por regresión lineal.

El efecto anti-inflamatorio de estos compuestos puede demostrarse en un ensayo de extravasación de pigmento azul Evans usando un ratón deficiente en inhibidor C1-esterasa. En este modelo, los ratones se dosifican con el compuesto de la presente invención, se inyecta el azul Evans por medio de la vena de la cola y la extravasación del pigmento azul se determina por medios de electrofotométricos de los extractos de tejido.

La capacidad de los compuestos de la actual invención para reducir o prevenir el síndrome de respuesta inflamatorio sistémico, por ejemplo, como se observa durante los procedimientos cardiovasculares en bombeo, pueden probarse en los sistemas de perfusión in vitro, o los procedimientos quirúrgicos en bombeo en mamíferos mas grandes, incluyendo perros y bovinos. Las lecturas para evaluar el beneficio de los compuestos de la invención incluyen, por ejemplo, pérdida de plaqueta reducida, complejos de célula de glóbulos blanco/plaqueta reducidos, niveles de neutrófilo elastasa reducidos en el plasma, activación reducida de factores de complemento, y activación reducida y/o consumo de las proteínas de activación por contacto (calicreína de plasma, factor XII, factor XI, cininógeno de alto peso molecular, inhibidores de C1-

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esterasa).

La utilidad de los compuestos de la actual invención para reducir o prevenir la morbilidad y/o mortalidad de sepsis puede evaluarse al inyectar un hospedador mamífero con bacterias o virus o extractos de estos y compuestos de la presente invención. Las lecturas típicas de la eficacia incluyen cambios en el LD50 y la conservación de presión sanguínea.

Los compuestos de la presente invención también pueden ser útiles como inhibidores de la serina proteasa adicional, notablemente la trombina humana, calicreína de plasma humano y plasmina humana. Debido a su acción inhibidora, estos compuestos están indicados para el uso en la prevención o tratamiento de reacciones fisiológicas, incluyendo coagulación de sangre, fibrinolisis, regulación de la presión sanguínea e inflamación, cicatrización de heridas catalizada por las clases anteriores de enzimas. Específicamente, los compuestos tienen utilidad como fármacos para el tratamiento de enfermedades que resultan de una actividad elevada de la trombina de la serina proteasa antes mencionada, tal como el infarto al miocardio, y como reactivos usados como anticoagulantes en el procesamiento de sangre para plasma para diagnóstico y otros propósitos comerciales.

Los compuestos de la presente invención se pueden

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administrar solos o en combinación con uno o más agentes terapéuticos adicionales. Estos incluyen otros agentes inhibidores de la coagulación o anticoagulantes, agentes inhibidores de las plaquetas o anti-plaquetas, inhibidores de la trombina o agentes trombolíticos o fibrinolíticos.

Los compuestos se administran a un mamífero en una cantidad terapéuticamente efectiva. Por "cantidad terapéuticamente efectiva" significa una cantidad de un compuesto de la presente invención que, cuando se administra solo o en combinación con un agente terapéutico adicional a un mamífero, es efectivo para tratar (esto es, prevenir, inhibir o mejorar) la condición de enfermedad tromboembólica y/o inflamatoria o tratar el avance de la enfermedad en un hospedador.

Los compuestos de la invención se administran preferiblemente solos a un mamífero a una cantidad terapéuticamente efectiva. Sin embargo, los compuestos de la invención también pueden administrarse en combinación con un agente terapéutico adicional, como se define abajo, a un mamífero en una cantidad terapéuticamente efectiva. Cuando se administran en combinación, la combinación de compuestos es preferiblemente pero no necesariamente, una combinación sinérgica. La sinergia, como se describe por Chou and Talalay, Adv. Enzyme Regul. 1984, 22, 27-55, se presenta cuando el efecto (en este caso la inhibición del objetivo

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deseado) de los compuestos cuando se administran en combinación es mayor que el efecto aditivo de los compuestos cuando se administran solos como un agente sencillo. En general el efecto sinérgico es más claramente demostrado a concentraciones sub-óptimas de los compuestos. La sinergia puede estar en términos de citotoxidad inferior, efecto anticoagulante incrementado, o algún otro efecto benéfico de la combinación en comparación con los componentes individuales.

Por "administrado en combinación" o "terapia de combinación", significa que un compuesto de la presente invención y uno o más agentes terapéuticos adicionales, se administran concurrentemente al mamífero en tratamiento. Cuando se administran en combinación, cada componente se puede administrar al mismo tiempo o secuencialmente en cualquier orden a diferentes puntos en el tiempo. Así, cada componente se puede administrar separado pero suficientemente cercano en tiempo como para proporcionar el efecto terapéutico deseado.

Los compuestos que pueden administrarse en combinación con los compuestos la presente invención incluyen, pero no se limitan a, anticoagulantes, agentes antitrombina, agentes antiplaquetas, fibrinolíticos, agentes hipolipidémicos, agentes antihipertensivos y agentes anti-isquémicos.

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Otros agentes anti-coagulantes (o agentes inhibidores de la coagulación) que se pueden usar en combinación con los compuestos de esta invención, incluyen la warfarina y heparina (ya sea heparina sin fraccionar o cualquier heparina comercialmente disponible de bajo peso molecular por ejemplo, LOVENOX™), aprotinina, pentasacárido sintético, inhibidores de la trombina de acción directa incluyendo hirudina y argatroban, así como otros factores VIIa, VIIIa, IXa, Xa, XIa, trombina, TAFI, e inhibidores de fibrinógeno conocidos en la técnica.

El término agentes anti-plaquetas (o agentes inhibidores de las plaquetas), como se usa en la presente, se refiere a agentes que inhiben la función de las plaquetas, por ejemplo al inhibir la agregación, adhesión o secreción granular de las plaquetas. Tales agentes incluyen, pero no se limitan a, los diversos fármacos conocidos no esteroidales anti-inflamatorios (NSAIDS) tal como la aspirina, ibuprofeno, naproxeno, sulindac, indometacina, mefenamato, droxicam, diclofenaco, sulfinpirazona y piroxicam, incluyendo sales o profármacos farmacéuticamente aceptables de los mismos. Se prefieren de los NSAIDS, la aspirina (ácido acetilsalicílico o ASA), y el piroxicam. Otros agentes inhibidores de las plaquetas adecuados incluyen antagonistas IIb/IIIa (por ejemplo, tirofiban, eptifibatida, y abciximab), antagonistas de tromboxano-receptor A2 (por ejemplo, ifetroban), e

inhibidores de tromboxano-A2-sintetasa, inhibidores de la fosfodiesterasa-III (PDE-III) (por ejemplo, dipiridamol, cilostazol) e inhibidores PDE V (tal como sildenafil) y sales o profármacos farmacéuticamente aceptable de los mismos.

El término agentes antiplaquetas (o agentes inhibidores de plaqueta), como se usa en la presente, también se pretende que incluya antagonistas del receptor ADP (adenosina disfosfato), preferiblemente antagonistas de los receptores purinérgicos P_2Y_1 y P_2Y_{12} con P_2Y_{12} siendo aun más preferidos. Los antagonistas receptores P_2Y_{12} preferidos incluyen ticlopidina y clopidogrel, incluyendo sales o fármacos farmacéuticamente aceptables de los mismos. El Clopidogrel es aun el agente más preferido. Ticlopidina y clopidogrel también son compuestos preferidos ya que se conoce que son amigables con el tracto gastrointestinal en uso. Los compuestos de la presente invención también pueden dosificarse en combinación con aprotinina.

El término inhibidores de trombina (o agentes anti-trombina), como se usa en la presente, se refiere a inhibidores de la trombina de la serina proteasa. Al inhibir la trombina, se rompen diversos procesos mediados por la trombina, tal como la activación de plaquetas mediada por trombina (esto es, por ejemplo, la agregación de plaquetas, y/o la secreción granular del inhibidor-1 activador de plasminógeno y/o serotonina), activación celular endotelial,

reacciones inflamatorias y/o la formación de fibrina. Se conocen diversos inhibidores de la trombina por alguien con experiencia en la técnica, y se contemplan estos inhibidores para usarse en combinación con los compuestos actuales. Tales inhibidores incluyen, pero no se limitan a, derivados de boroarginina, boropéptidos, heparinas, hirudina, y argatroban, incluyendo sales y profármacos farmacéuticamente aceptables de los mismos. Los derivados de boroarginina y boropéptidos incluyen derivados de N-acetilo y péptido de ácido borónico, tal como derivados de ácido α-aminoborónico en la terminación "C" de lisina, ornitina, arginina, homoarginina y análogos correspondientes de isotiouronio del mismo. El término hirudina, como se usa en la presente, que incluye derivados o análogos apropiados de la hirudina, que se refieren en la presente como hirulogos, tal como la disulfatohirudina.

El término agentes trombolíticos (o fibrinolíticos), (o trombolíticos o fibrinolíticos) como se usa en la presente, se refiere a agentes que lisan los coágulos de sangre (trombos). Tales agentes incluyen al activador de plasminógeno de tejido (TPA, natural o recombinante) y formas modificadas del mismo, anistreplasa, urocinasa o estreptocinasa tenecteplasa (TNK), lanoteplasa (nPA), inhibidores del factor VIIa, inhibidores PAI-I (esto es, inactivadores de los inhibidores de activador de

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plasminógeno de tejidos), inhibidores de alfa-2-antiplasmina y complejo activador de estreptocinasa de plasminógeno anisoilado, incluyendo sales o profármacos farmacéuticamente aceptables del mismo. El término anistreplasa, como se usa en la presente, se refiere al complejo activador de la estreptocinasa del plasminógeno anisoilado como se describe, por ejemplo, en la solicitud de patente europea No 028,489, la descripción de la cual se incorpora en la presente como referencia. El término urocinasa, como se usa en la presente, pretende referirse a la urocinasa de cadena dual y simple, refiriéndose a la última también como prourocinasa.

Los ejemplos de agentes antiarrítmicos apropiados para usarse en combinación con los compuestos presentes incluyen: agentes de clase I (tal como propafenona); agentes de clase II (tal como carvadiol y propranolol); agentes de clase III (tal como sotalol, dofetilida, amiodarona, azimilida, e ibutilida); agentes de clase IV (tal como ditiazem y verapamil); abridores del canal K^+ tales como inhibidores I_{Ach}, e inhibidores I_{Kur} (por ejemplo, los compuestos tales como aquellos descritos en el documento WO 01/40231).

El término agentes antihipertensivos, como se describe en la presente incluye: bloqueadores alfa adrenérgico; bloqueadores beta adrenérgicos, bloqueadores del canal de calcio (por ejemplo, diltiazem, verapamil,

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nifedipina, amlodipina y mybefradil); diuréticos (por ejemplo, clorotiazida, hidroclorotiazida, flumetiazida, hidroflumetiazida, bendroflumentiazida, metilclorotiazida, triclorometiazida, politiazida, benzitiazida, ácido etacrínico tricrinafen, clortalidona, furosemida, musolimina, bumetanida, triamtreneno, amilorida, espironolactona); inhibidores de renina; inhibidores de la enzima que convierte la angiotensina (ACE) (por ejemplo, captropil, lisinopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); antagonistas del receptor II de angiotensina (por ejemplo, irbestatina, losartan, valsartan); antagonistas del receptor ET (por ejemplo, sitaxsentan, atrsentan y compuestos descritos en la patentes de E.U. Nos: 5,612,359 y 6,043,265); antagonistas ET/AII duales (por ejemplo, los compuestos descritos en WO 00/01389); inhibidores de endopeptidasa neutral (NEP); inhibidores de vasopeptidasa (dual ACE/NEP, por ejemplo, omapatrilat, gemopatrilat, nitratos); y β-bloqueadores (por ejemplo, propanolol, nadolo, o carvedilol).

Los ejemplos de glicósidos cardiacos apropiados para usarse en combinación con los compuestos la presente invención incluyen digitalis y ouabaina.

Los ejemplos de antagonistas del receptor mineralocorticoide apropiados para usarse en combinación para los compuestos la presente invención incluyen esprionolactona

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y eplirinona.

Los ejemplos de los agentes reductores del colesterol/lípidos apropiados y terapias de perfil de lípido para usarse en combinación de los compuestos la presente invención incluyen: inhibidores de la HMG-CoA reductasa (por ejemplo, pravastatina, lovastatina, atorvastatina, simvastatina, fluvastatina, NK-104 (a.k.a. itavastina o nisvastatina o nisbastatina y ZD-4522 (a.k.a. rosuvastatina o atavastatina o visastatina); e inhibidores de la escualeno sintetasa; fibratos; secuestrantes del ácido biliar (tal como questram); inhibidores ACAT; inhibidores MTP; inhibidores de lipooxigenasa, inhibidores de absorción de colesterol e inhibidores de la proteína transferida por éster de colesterol (por ejemplo CP-529414).

Los ejemplos de agentes antidiabéticos apropiados para usarse en combinación para los compuestos la presente invención incluyen: biguanidas (por ejemplo, metformina); inhibidores de glucosidasa (por ejemplo, acarbosa); insulinas (incluyendo secretagogos de insulina o sensibilizadores de insulina); meglitidinas (por ejemplo, repaglinida); sulfonilureas (por ejemplo, glimepirida, gliburida y glipizida); combinaciones biguanida/gliburida (por ejemplo, glucovance), tiozolidindionas (por ejemplo, troglitazona, rosiglitazona y pioglitazona), agonistas alfa PPAR, agonistas gamma PPAR, agonistas duales alfa/gamma PPAR, inhibidores

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SGLT2, inhibidores de la proteína de enlace ácido graso (aP2) tal como aquellos descritos en WO 00/59506, péptido 1 tipo glucagon (GLP-1), e inhibidores de la dipeptidil peptidasa IV (DP4).

Los ejemplos de agentes anti-depresión apropiados para usarse en combinación con los compuestos la presente invención incluyen nefazodona y sertralina.

Los ejemplos de agentes anti-inflamatorios apropiados para usarse en combinación con los compuestos la presente invención incluyen: prednisona, dexametasona, enbrel; inhibidores de la proteína tirosina cinasa (PTK); inhibidores de cicloxigenasa (incluyendo NSAIDs, e inhibidores COX-1 y/o COX-2); aspirina; indometacina; ibuprofeno; prioxicam; naproxeno; celecoxib; y/o rofecoxib.

Los ejemplos de agentes anti-osteoporosis apropiados para usarse en combinación con los compuestos la presente invención incluyen alendronato y raloxifeno.

Los ejemplos de las terapias de reemplazo de hormonas apropiados para usarse en combinación con los compuestos la presente invención incluyen estrógeno (por ejemplo, estrógenos conjugados) y estradiol.

Los ejemplos de agentes antiobesidad apropiados para usarse en combinación con los compuestos la presente invención incluyen orlistat e inhibidores aP2 (tal como aquellos descritos en el documento WO00/59506).

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Los ejemplos de agentes anti-ansiedad apropiados para usarse en combinación con los compuestos la presente invención incluyen diazepam, lorazepam, buspirona y pamoato de hidroxizina.

Los ejemplos de agentes anti-ansiedad apropiados para usarse en combinación con los compuestos la presente invención incluyen diazepam, lorazepam, buspirona y pamoato de hidroxizina.

Los ejemplos de agentes anti-proliferativos apropiados para usarse en combinación con los compuestos la presente invención incluyen ciclosporina A, paclitaxel, adriamicina, epitilonas cisplatina, y carboplatina.

Los ejemplos de agentes de enfermedad de reflujo gastroesofagal y anti-úlcera para usarse en combinación con los compuestos la presente invención incluyen famotidina, ranitidina y omeprazol.

La administración de los compuestos de la presente invención (esto es, un primer agente terapéutico) en combinación con al menos un agente terapéutico adicional (esto es, un segundo agente terapéutico) preferiblemente proporciona una ventaja de eficacia sobre los compuestos y agentes solos, preferiblemente mientras permiten el uso de dosis más bajas de cada uno. Una dosis más baja minimiza el potencial de efectos colaterales proporcionando por ello un margen incrementado de seguridad. Se prefiere que al menos

uno de los agentes terapéuticos se administren en una dosis sub-terapéutica. Es aun más preferido que todos los agentes terapéuticos se administren en dosis sub-terapéuticas. Sub-terapéuticos se pretende que signifique una cantidad de un agente terapéutico que por sí mismo no da el efecto terapéutico deseado para la condición o enfermedad a tratarse. La combinación sinérgica se pretende que signifique que el efecto observado de la combinación es mayor que la suma de los agentes individuales administrados solos.

Los compuestos de la presente invención también son útiles como compuestos estándar o de referencia, por ejemplo como un estándar o control de calidad, en pruebas o ensayos que involucran la inhibición de trombina, factor VIIa, IXa, Xa, XIa y/o calicreína de plasma. Tales compuestos se pueden suministrar en un kit comercial, por ejemplo, para su uso en investigación farmacéutica que involucra trombina, factor VIIa, IXa, Xa, XIa y/o calicreína de plasma. Por ejemplo, un compuesto de la presente invención, se puede usar como una referencia en un ensayo, para comparar su actividad conocida con un compuesto con una actividad desconocida. Esto aseguraría al experimentador que el ensayo se lleve a cabo adecuadamente, y proporciona una base para comparación, especialmente si el compuesto de prueba fue un derivado del compuesto de referencia. Cuando se desarrollan nuevos ensayos o protocolos, los compuestos de conformidad con la presente

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invención se pueden usar para probar su efectividad.

Los compuestos de la presente invención se pueden usar también en ensayos de diagnóstico que involucran trombina, factor VIIa, IXa, Xa, XIa y/o calicreína de plasma. Por ejemplo, la presencia de trombina, factor VIIa, IXa, Xa, XIa y/o calicreína de plasma en una muestra desconocida, se puede determinar por la adición del substrato cromogénico relevante, por ejemplo S2366 para el factor XIa a una serie de soluciones que contienen la muestra de prueba y opcionalmente uno de los compuestos de la presente invención. Si se observa la producción de pNA en las soluciones que contienen la muestra de prueba, pero no en presencia de un compuesto de la presente invención, entonces se concluiría que el factor XIa estaba presente.

Los compuestos selectivos y extremadamente potentes de la presente invención, aquellos que tienen valores K_i menores a o iguales a 0.001 μM contra la proteasa objetivo y mayores a o iguales a 0.1 μM contra otras proteasas, también pueden usarse en ensayos de diagnóstico que involucran la cuantificación de trombina, factor VIIa, IXa, Xa, XIa y/o calicreína de plasma en muestras de suero. Por ejemplo, la cantidad de factor XIa en muestras de suero podrá determinarse por la titulación cuidadosa de la actividad de proteasa en presencia de un substrato cromogénico relevante S2366, con un inhibidor de factor XIa potente y selectivo de

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la presente invención.

La presente invención también abarca un artículo de manufactura. Como se usa en la presente el artículo de manufactura se pretende que incluya, pero no se limite a, kits y empaques. El artículo de manufactura de la presente invención, comprende: (a) un primer recipiente (b) una composición farmacéutica localizada dentro de primer recipiente, en donde la composición comprende: un primer agente terapéutico que comprende: un compuesto de la presente invención o una forma de sal farmacéuticamente aceptable del mismo y (c) un inserto de empaque que establece que la composición farmacéutica puede usarse para el tratamiento de un trastorno tromboembólico y/o inflamatorio (como se define previamente). En otra modalidad el inserto de empaque establece que la composición farmacéutica puede usarse en combinación (como se define previamente) con un segundo agente terapéutico para tratar un trastorno tromboembólico y/o inflamatorio. El artículo de manufactura puede comprender además: (d) un segundo recipiente en donde los componentes (a) y (b) se localizan dentro del segundo recipiente y el componente (c) se localiza dentro o fuera del segundo recipiente. Localizado dentro del primero y segundo recipiente significa que el recipiente respectivo mantiene el artículo dentro de sus límites.

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El primer recipiente es un receptáculo usado para mantener una composición farmacéutica. Este recipiente puede ser para fabricación, almacenamiento, embarque y/o venta a granel/individual. El primer recipiente se pretende que cubra una botella, frasco, vial, matraz, jeringa, tubo (por ejemplo, para una preparación de cremas) o cualquier otro recipiente usado para la fabricación, almacenamiento mantenimiento o distribución de un producto farmacéutico.

El segundo recipiente es uno usado para mantener el primer recipiente y opcionalmente el inserto del empaque. Los ejemplos del segundo recipiente incluyen, pero no se limitan a cajas (por ejemplo, cajas de cartón o plástico), canastas, cartones, bolsas (por ejemplo, bolsas de papel o plástico), sacos y costales. El inserto de empaque puede unirse físicamente al exterior del primer recipiente por medio de cinta, pegamento, grapas u otros métodos de unión, o puede quedarse dentro del segundo recipiente sin ningún medio físico de sujeción al primer recipiente. Alternativamente, el inserto de empaque se localiza en el exterior del segundo recipiente. Cuando se localiza en el exterior del segundo recipiente, se prefiere que el inserto de empaque se una físicamente por medio de cinta, pegamento, grapa u otro método de unión. Alternativamente, puede estar adyacente o tocar el exterior del segundo recipiente sin unirse físicamente.

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El inserto de empaque es una etiqueta, tarjeta, marcador, etc, que menciona la información con relación a la composición farmacéutica localizada dentro del primer recipiente. La información mencionada usualmente se determinará por la agencia reguladora del gobierno en el área en el cual el articulo de fabricación se va a vender (por ejemplo, la United States Food and Drug Administration). Preferiblemente, el inserto del empaque menciona específicamente las indicaciones para las cuales la composición farmacéutica se ha aprobado. El inserto de empaque puede hacerse de cualquier material en el cual una persona pueda leer la información contenida en éste. Preferiblemente, el inserto de empaque es un material imprimible (por ejemplo, papel, plástico, cartón, papel aluminio, papel con adhesivo, o plástico etc.) en el cual se ha formado la información deseada (por ejemplo, impreso o aplicado).

DOSIFICACIÓN Y FORMULACIÓN

Los compuestos de esta invención se pueden administrar en formas de dosificación oral tales como tabletas, cápsulas (cada una de las cuales incluye formulaciones de liberación programada o liberación sostenida), píldoras, polvos, gránulos, elíxires, tinturas, suspensiones, jarabes y emulsiones. También se pueden

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administrar en forma intravenosa (bolo o infusión), intraperitoneal, subcutánea, o intramuscular, todas usando formas de dosificación bien conocidas por aquellos de habilidad ordinaria en las artes farmacéuticas. Se pueden administrar solos, pero generalmente se administrarán con un portador farmacéutico seleccionado sobre la base de la vía escogida de administración y la práctica farmacéutica estándar.

El régimen de dosificación para los compuestos de la presente invención, variará, por supuesto, dependiendo de factores conocidos, tales como las características farmacodinámicas del agente en particular y su modo y vía de administración, la especie, edad, sexo, salud, condición médica, y peso del receptor; la naturaleza y extensión de los síntomas, el tipo de tratamiento concurrente, la frecuencia de tratamiento, la vía de administración, la función renal y hepática del paciente y el efecto deseado. Un médico o un veterinario puede determinar y prescribir la cantidad efectiva del fármaco requerido para prevenir, contrarrestar o detener el progreso del padecimiento tromboembólico.

A manera de guía general, la dosificación diaria oral de cada ingrediente activo, cuando se usa para los efectos indicados, estará entre alrededor de 0.001 a 1000 mg/kg de peso corporal, preferiblemente entre alrededor de 0.01 a 100 mg/kg de peso corporal por día, y más

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preferiblemente entre alrededor de 1.0 a 20 mg/kg/día. Intravenosamente, las dosificaciones más preferidas estarán desde alrededor de 1 a alrededor de 10 mg/kg/minuto durante una infusión a velocidad constante. Los compuestos de esta invención se pueden administrar en una dosificación diaria simple, o la dosificación diaria total se puede administrar en dosis divididas de dos, tres ó cuatro veces diariamente.

Los compuestos de esta invención se pueden administrar en forma intranasal mediante el uso tópico de vehículos intranasales adecuados, o por medio de vías transdérmicas usando parches transdérmicos para la piel. Cuando se administran en forma de un sistema de suministro transdérmico, la administración de la dosis será, por supuesto, continua más que intermitente a lo largo del régimen de dosificación.

Los compuestos se administran típicamente en mezcla con diluyentes, excipientes o portadores farmacéuticamente adecuados (referidos colectivamente en la presente como portadores farmacéuticos) seleccionados adecuadamente con respecto a la forma pretendida de administración, esto es, tabletas orales, cápsulas, elíxires, jarabes, y similares, y consistente con las prácticas farmacéuticas convencionales.

Por ejemplo, para administración oral en forma de una tableta o cápsula, el componente del fármaco activo se

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puede combinar con un portador oral no tóxico, farmacéuticamente aceptable, inerte, tal como la lactosa, almidón, sacarosa, glucosa, metilcelulosa, estearato de magnesio, fosfato de dicalcio, sulfato de calcio, manitol, sorbitol y similares; para administración oral en forma líquida, los componentes del fármaco oral, se pueden combinar con cualquier portador inerte oral, no tóxico, farmacéuticamente aceptable, tal como el etanol, glicerol, agua y similares. Además, cuando se desea o es necesario, se pueden también incorporar aglutinantes, lubricantes, agentes desintegrantes, y agentes colorantes adecuados dentro de la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales, tales como glucosa, o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas, tales como acacia, tragacanto o alginato de sodio, carboximetilcelulosa, polietilenglicol, ceras y similares. Los lubricantes usados en estas formas de dosificación incluyen oleato de sodio, estearato de sodio, estearato de magnesio, benzoato de sodio, acetato de sodio, cloruro de sodio, y similares. Los desintegradores incluyen, sin limitación, almidón, metil celulosa, agar, bentonita, goma xantana, y similares.

Los compuestos de la presente invención también se pueden administrar en forma de sistemas de suministro de liposomas tal como vesículas pequeñas unilamelares, vesículas

grandes multilamelares, y vesículas multilamelares. Los liposomas se pueden formar de una diversidad de fosfolípidos tal como el colesterol, estearilamina, y fosfatidilcolinas.

Los compuestos de la presente invención también se pueden acoplar con polímeros solubles como portadores de fármacos objetivos. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamida-fenol, polihidroxietilaspartamidafenol, u óxido de polietileno-polilisina sustituida con residuos de palmitoilo. Además, los compuestos de la presente invención, se pueden acoplar a una diversidad de polímeros biodegradables útiles en alcanzar la liberación controlada de un fármaco, por ejemplo, ácido poliláctico, ácido poliglicólico, copolímeros de ácido poliláctico y poliglicólico, poliepsilon caprolactona, ácido polihidroxibutírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacilatos, y copolímeros de bloque anfipáticos o reticulados de hidrogeles.

Las formas de dosificaciones (composiciones farmacéuticas) adecuadas para administración, pueden contener desde alrededor de 1 miligramo hasta alrededor de 100 miligramos de ingrediente activo por unidad de dosificación. En estas composiciones farmacéuticas, el ingrediente activo estará presente ordinariamente en una cantidad de alrededor de 0.5-95% en peso con base en el peso total de la

composición.

Las cápsulas de gelatina pueden contener el ingrediente activo y portadores en polvo tal como lactosa, almidón, derivados de celulosa, estearato de magnesio, ácido esteárico, y similares. Se pueden usar diluyentes similares para hacer tabletas comprimidas. Las tabletas y cápsulas se pueden fabricar como productos de liberación sostenida, para proporcionar la liberación continua del medicamento durante un periodo de horas. Las tabletas comprimidas pueden ser recubiertas con azúcar o recubiertas con una película para ocultar cualquier sabor desagradable y proteger la tableta de la atmósfera, o recubrir de forma entérica para la desintegración selectiva en el tracto gastrointestinal.

Las formas de dosificación líquidas para administración oral, pueden contener coloración y saborizante para incrementar la aceptación del paciente.

En general, el agua, un aceite adecuado, solución salina, dextrosa acuosa (glucosa), y soluciones relacionadas de azúcar y glicoles tales como el propilenglicol o los polietilenglicoles, son portadores adecuados para soluciones parenterales. Las soluciones para administración parenteral contienen preferiblemente una sal soluble en agua del ingrediente activo, agentes estabilizadores adecuados y, si es necesario, sustancias amortiguadoras. Los agentes antioxidantes tales como el bisulfito de sodio, sulfito de

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sodio, o ácido ascórbico, ya sea solos o combinados, son agentes adecuados de estabilización. También se usan el ácido cítrico y sus sales y el EDTA de sodio. Además, las soluciones parenterales pueden contener conservadores tales como el cloruro de benzalconio, metil o propil-paraben y clorobutanol.

Los portadores farmacéuticos adecuados se describen en Remington's Pharmaceutical Sciences, Mack Publishing Company, un texto de referencia estándar en este campo.

En donde se combinan los compuestos de esta invención con otros agentes anticoagulantes, por ejemplo, una dosificación diaria puede ser de alrededor de 0.1 a 100 miligramos de compuesto de la presente invención y alrededor de 1 a 7.5 miligramos del segundo anticoagulante, por kilogramo de peso corporal del paciente. Para una fórmula de dosis en tabletas, los compuestos de esta invención pueden estar generalmente presentes en una cantidad desde alrededor de 5 a 10 miligramos por unidad de dosificación, y el segundo anticoagulante en una cantidad de alrededor de 1 hasta 5 miligramos por unidad de dosificación.

En donde se administran los compuestos de la presente invención en combinación con un agente anti-plaquetas, a manera de guía general, típicamente una dosificación diaria puede ser de alrededor de 0.01 a 25

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miligramos del compuesto de la presente invención y alrededor de 50 a 150 miligramos del agente anti-plaqueta, preferiblemente alrededor de 0.1 a 1 miligramos del compuesto de la Fórmula I y alrededor de 1 a 3 miligramos de agentes anti-plaqueta por kilogramo de peso corporal del paciente.

En donde los compuestos de la presente invención se administran en combinación con el agente trombolítico, una dosificación diaria típicamente puede ser de alrededor de 0.1 a 1 miligramo del compuesto de la presente invención, por kilogramo de peso corporal del paciente y, en el caso de los agentes trombolíticos, la dosificación usual del agente trombolítico cuando se administra solo, se puede reducir por alrededor de 70-80% cuando se administra con un compuesto de la presente invención.

En donde se administran dos o más de los agentes terapéuticos segundos anteriores con el compuesto de la presente invención, se pueden reducir generalmente la cantidad de cada componente en una dosificación diaria típica, con relación a la dosis usual del agente cuando se administra solo, en vista del efecto aditivo o sinérgico de los agentes terapéuticos cuando se administra en combinación.

Particularmente cuando se suministra como una unidad de dosificación simple, existe un potencial para una interacción química entre los ingredientes activos combinados. Por esta razón, cuando se combinan el compuesto

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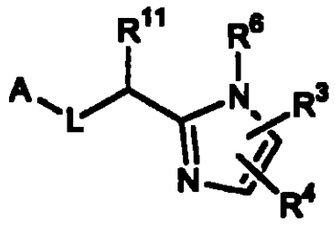
de la Fórmula I y un segundo agente terapéutico en una unidad de dosificación simple, estos se formulan de manera que no obstante que los ingredientes activos se combinen en una unidad de dosificación simple, el contacto físico entre los ingredientes activos se minimice (esto es, se reduce). Por ejemplo, un ingrediente activo se puede recubrir de forma entérica. Al recubrir de forma entérica uno de los ingredientes activos, es posible no solamente minimizar el contacto entre los ingredientes activos combinados, sino también es posible controlar la liberación de uno de estos componentes en el tracto gastrointestinal, de manera tal que uno de estos componentes no se libere en el estómago sino más bien se libere en los intestinos. Uno de los ingredientes activos se puede también recubrir con un material que afecte una liberación sostenida a través del tracto gastrointestinal, y sirva también para minimizar el contacto físico entre los ingredientes activos combinados. Además, el componente de liberación sostenida puede recubrirse adicionalmente de forma entérica de manera tal que la liberación de este componente suceda solamente en el intestino. Todavía otro enfoque, involucraría la formulación de un producto de combinación en el cual un componente se recubre con un polímero de liberación entérica y/o sostenida, y el otro componente también se recubre con un polímero tal como uno de grado de baja viscosidad de hidroxipropil

metilcelulosa (HPMC) u otros materiales apropiados como se conocen en la técnica, con objeto de separar además los componentes activos. El recubrimiento de polímero sirve para formar una barrera adicional a la interacción con el otro componente.

Estas así como otras formas de minimizar el contacto entre los componentes de los productos de combinación de la presente invención, ya sea administrados en una forma de dosis simple o administrados en forma separadas pero al mismo tiempo por la misma forma, serán fácilmente aparentes para aquellos con habilidad en la técnica, una vez equipados con la presente descripción.

REIVINDICACIONES

1. Un compuesto de fórmula (I):



(I)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, caracterizado porque:

A es carbociclo C_{3-10} substituido con 0-1 R^1 y 0-3 R^2, o con un heterociclo de 5 hasta 12 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no está unido a L por medio de cualesquiera de los átomos de nitrógeno en el anillo A;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$,

$-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)_pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, o $-C(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-NH$(alquilo C_1-C_3), $-N$(alquilo C_1-$C_3)_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH_2)_rNR^7R^8$, $-(CH_2)_rNR^7CO_2R^a$, $-CH_2NH_2$, $-CH_2NH$(alquilo C_{1-3}), $-CH_2N$(alquilo $C_{1-3})_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH$(alquilo C_1-C_3), $-CH_2CH_2N$(alquilo $C_{1-3})_2$, $-CH$(alquilo C_{1-4})NH_2, $-C$(alquilo $C_{1-4})_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-ciclopropilo, o alquilo C_{1-6} substituido con 0-1 R^{1a};

R^{1a} es H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, $-NR^8SO_2R^c$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^2 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} substituido con 0-2 R^{2a}, alquenilo C_{2-6} substituido con 0-2 R^{2a}, alquinilo C_{2-6} substituido con 0-2 R^{2a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{2b}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{2b};

R^{2a} es, independientemente cada que se presenta, H, F,

Cl, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{2b} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^C$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4}-;

alternativamente, cuando los grupos R^1 y R^2 son substituidos en átomos de anillo adyacente, estos pueden tomarse junto con los átomos en el anillo al cual se enlazan para formar un carbociclo o heterociclo de 5 a 7 miembros que comprende: átomos de carbono y 0-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el carbociclo o heterociclo está substituido con 0-2 R^{2b};

R^3 es $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo de 5- a 10- miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, -

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$(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-C(O)-$alquilo C_{1-4}, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, haloalquilo C_{1-4}, haloalcoxi $C_{1-4}-$, alquilo C_{1-6} substituido por R^{3d}, alquenilo C_{2-6} substituido por R^{3d}, alquinilo C_{2-6} substituido por R^{3d}, cicloalquilo C_{3-6} substituido por 0-1 R^{3d}, $-(CH_2)_r-$carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r-$heterociclo de 5- hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3d};

alternativamente, cuando dos grupos R^{3a} se localizan en átomos adyacentes, estos pueden tomarse junto con los átomos a los cuales están enlazados para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3d};

R^{3b} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r-$carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el

heterociclo es substituido con 0-3 R^{3d};

R^{3c} es, independientemente cada que se presenta, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3d};

R^{3d} es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-S(O)_pR^C$, $-(CF_2)_rCF_3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, alquinilo C_{2-6} substituido con 0-2 R^e, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^{4b}, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4

heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{4a} es, independientemente cada que se presenta, H, F, =O, alquilo C_{1-6}, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^c$, $-S(O)R^c$, o $-S(O)_2R^c$;

R^{4b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^c$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4}-;

alternativamente, los grupos R^3 y R^4 cuando se localizan en átomos adyacentes, pueden tomarse juntos para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3d};

R^6 es H;

R^7 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n-$ carbociclo C_{3-10}, $-(CH_2)_n-$(heteroarilo de 5-10 miembros), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$OC(O)-$(arilo C_{6-10}); en donde los alquilo, carbociclo, heteroarilo, y arilo están substituidos opcionalmente con 0-2 R^f;

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R^8 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo, o $-(CH_2)_n$- heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los alquilo, fenilo y heterociclo están substituidos opcionalmente con 0-2 R^f;

alternativamente, R^7 y R^8, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^d;

R^{8a} es, independientemente cada que se presenta, H, OH, alquilo C_{1-6}, alcoxi C_{1-4}, (arilo C_{6-10})-alcoxi C_{1-4}, $-(CH_2)_n$-fenilo, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(alquilo C_{1-4}), o $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(arilo C_{6-10}); en donde el fenilo, arilo, y heteroarilo están opcionalmente substituidos con 0-2 R^f;

R^9 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo; en donde el alquilo y fenilo están substituidos opcionalmente con 0-2 R^f;

R^{9a} es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

alternativamente, R^8 y R^9, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en

donde el heterociclo está substituido con 0-2 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, alquenilo C_{2-6} substituido con 0-3 R^{10a}, alquinilo C_{2-6} substituido con 0-3 R^{10a}, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

R^{10a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^c-$, $-S(O)R^c$, o $-S(O)_2R^c$;

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CR^{14}R^{15})_r-$ carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CR^{14}R^{15})_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{11b};

R^{11a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, CF_3, SR^a, F, CN, NO_2, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^c$, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi $C_{1-4}-$, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4

heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^d;

R^{11b} es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^c$, $-SO_2R^c$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, $-(CH_2)r-$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)r-$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^d;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales están enlazados para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g;

R^{14} y R^{15} son, independientemente cada que se presentan, H, F, o alquilo C_{1-4};

alternativamente, R^{14} se combina con R^{15} para formar =O;

R^a es, independientemente cada que se presenta, H, CF_3, alquilo C_{1-6}, $-(CH_2)_r-$ cicloalquilo C_{3-7}, $-(CH_2)_r-$ arilo C_{6-10}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los grupos cicloalquilo, arilo y heterociclo

son opcionalmente substituidos con 0-2 R^f;

R^b es, independientemente cada que se presenta, CF_3, OH, alcoxi C_{1-4}, alquilo C_{1-6} $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^c es, independientemente cada que se presenta, CF_3, alquilo C_{1-6} substituido con 0-2 R^f, cicloalquilo C_{3-6} substituido con 0-2 R^f, arilo C_{6-10}, heteroarilo de 5 hasta 10 miembros, (arilo C_{6-10})-alquilo C_{1-4}, o (heteroarilo de 5 hasta 10 miembros)-alquilo C_{1-4}, en donde los grupos arilo y heteroarilo son opcionalmente substituidos con 0-3 R^f;

R^d es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, o alquinilo C_{2-6} substituido con 0-2 R^e;

R^e es, independientemente cada que se presenta, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^f es, independientemente cada que se presenta, H, =O, $-(CH_2)_r-OR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2-$alquilo C_{1-4}, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2-$fenilo, $-S(O)_2CF_3$, $-S(O)_p-$alquilo C_{1-4}, $-S(O)_p-$fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, o $-(CH_2)_n-$fenilo;

R^g es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n-$fenilo;

n, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4;

p, cada que se presenta, se selecciona de 0, 1, y 2;

r, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4; y

s, cada que se presenta, se selecciona de 1, 2, 3, y 4;

con la condición de que:

(a). cuando L es $-C(O)NH-$, R^3 no es 2,4-diclorofenilo, 4-nitrofenilo o pentafluorofenilo;

(b). cuando L es $-C(O)NH-$, R^{11} no es $-CH_2-$(3-indolilo), $-(CH_2)_4NHCO_2$(t-Bu) o $-(CH_2)_4NH_2$.

2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque:

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2CONR^{10}-$, o $-NR^{10}COCH_2-$;

R^3 es $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r-$fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r-$naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)r-$

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indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_r-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{11a}, alquenilo C_{2-6} con 0-2 R^{11a}, alquinilo C_{2-6} substituido con 0-2 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b}.

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3. Un compuesto de conformidad con la reivindicación 1, caracterizado porque:

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, -NHEt, $-NHCO_2(t\text{-}Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a o $-CH_2R^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)_r$-fenilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, naftilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, indanilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, CF_3, OMe, NH_2, CO_2H, CO_2Me, CO_2Et, $-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

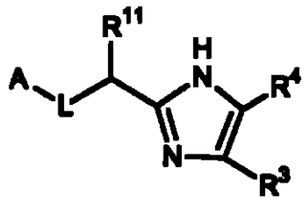
R^{10} es, independientemente cada que se presenta, H, Me, bencilo, fenetilo, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, o $-CH_2CH_2CONHCH_2CH_2Ph$; y

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo

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substituido con 0-2 R^{11b}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{11b}.

4. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de la Fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, en donde:

A está substituido con 0-1 R^1 y 0-2 R^2 y se selecciona de: cicloalquilo C_{3-7}, fenilo naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

L es -C(O)NH- o -NHC(O)-;

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t\text{-}Bu)$, -

$NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, fenilo substituido con 0-2 R^{3a}, naftilo substituido con 0-2 R^{3a}, indanilo substituido con 0-2 R^{3a}, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-2 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{3a};

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{4b};

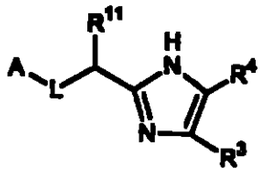
R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$ heteroarilo de 5 hasta 10 miembros substituidos con 0-2 R^{11b} y seleccionados de tiazolilo, oxazolilo, triazolilo, tetrazolilo, imidazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, benzimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, tetrahidroquinolinilo, y tetrahidroisoquinolinilo; y

R^{11b} es, independientemente cada que se presenta, H, F,

Cl, Br, CF_3, OMe, OEt, O(i-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, alquilo C_1-C_4-, Ph, o Bn;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos al cual están enlazados para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g.

5. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de la Fórmula (II):



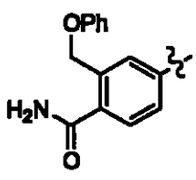
(II)

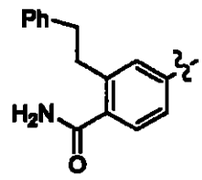
o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, en donde:

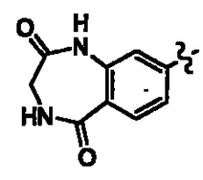
A es 4-CH_2NH_2-ciclohexilo, 4-CO_2Me-ciclohexilo, 4-$CONH_2$-ciclohexilo, 4-$NHCO_2$(t-Bu)-ciclohexilo, 4-$NHCO_2$Bn-ciclohexilo, fenilo, 4-Me-fenilo, 3-OMe-fenilo, 4-CH_2NH_2-fenilo, 3-$CONH_2$-fenilo, 4-$CONH_2$-fenilo, 3-amidino-fenilo, 4-amidino-fenilo, 2-F-4-Me-fenilo, 2-Bn-4-CH_2NH_2-fenilo, 4-SO_2NH_2-fenilo, 2-F-5-OMe-fenilo, 2-F-4-Cl-fenilo, 2-F-4-CH_2NH_2-fenilo, 2-F-4-$CONH_2$-fenilo, 2-Cl-4-$CONH_2$-fenilo, 2-Et-4-CH_2NH_2-fenilo, 2-NHEt-4-

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CH_2NH_2-fenilo, 2-OMe-4-$CONH_2$-fenilo, 3-OMe-4-$CONH_2$-fenilo, 1,2,3,4-tetrahidronaft-2-ilo, 3-Cl-tien-2-ilo, indol-5-ilo, indol-6-ilo, indazol-6-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-indazol-5-ilo, 1-Me-3-NH_2-indazol-6-ilo, 3-NH_2-benzisoxazol-6-ilo, 1,2,3,4-tetrahidroisoquinolin-6-ilo, 1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-COPh-1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-CO_2Bn-1,2,3,4-tetrahidroisoquinolin-3-ilo, 1,2,3,4-tetrahidroisoquinolin-1-on-6-ilo, 2H-isoquinolin-1-on-6-ilo, isoquinolin-6-ilo, 1-NH_2-isoquinolin-6-ilo, 1-NH_2-3-Me-isoquinolin-6-ilo, 1-NH_2-5,6,7,8-tetrahidroisoquinolin-6-ilo, 4-NH_2-quinazolin-7-ilo, 3H-quinazolin-4-on-7-ilo,





o


R^3 es CO_2H, CO_2Me, -C(O)$NHCH_2CO_2H$, -C(O)$NHCH_2CO_2Et$, -C(O)NH_2, -C(O)NHMe, -C(O)NHBn, fenilo, fenetilo, -(CH=CH)-fenilo, 3-bifenilo, 4-bifenilo, 3,4-metilendioxifenilo, 1-naftilo, 2-naftilo, 3-NH_2-fenilo, 3-NMe_2-fenilo, 4-OPh-fenilo, 4-OBn-fenilo, 4-(t-butoximetil)-fenilo, 4-SO_2Me-fenilo, 3-CN-fenilo, 4-CN-fenilo, 3-F-fenilo, 4-F-fenilo, 3-Cl-fenilo, 4-Cl-fenilo, 3-Br-fenilo, 4-Br-fenilo, 3-OH-fenilo, 4-OH-fenilo, 2-OMe-fenilo, 3-OMe-fenilo, 4-OMe-fenilo, 3-CF_3-fenilo, 4-

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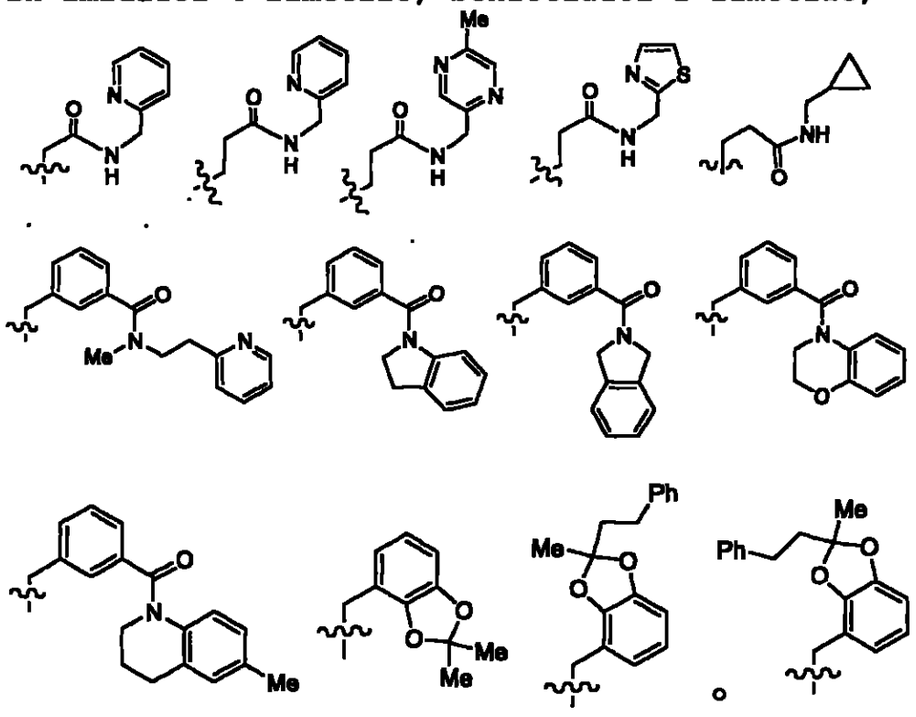
CF_3-fenilo, 3-CO_2H-fenilo, 4-CO_2H-fenilo, 3-CO_2Me-fenilo, 4-CO_2Me-fenilo, 3-CH_2CO_2H-fenilo, 4-CH_2CO_2H-fenilo, 4-CH_2CO_2Me-fenilo, 3-CH_2CO_2Et-fenilo, 4-CH_2CO_2Et-fenilo, 3-$CONH_2$-fenilo, 4-$CONH_2$-fenilo, 3-CH_2CONH_2-fenilo, 4-CH_2CONH_2-fenilo, 4-CONHMe-fenilo, 4-$CONMe_2$-fenilo, 4-amidino-fenilo, 3-NHCOMe-fenilo, 4-NHCOMe-fenilo, 4-$NHCO_2Me$-fenilo 4-SO_2NH_2-fenilo, 3-$NHSO_2Me$-fenilo, 4-$NHSO_2Me$-fenilo, 2,4-diF-fenilo, 3-F-4-CN-fenilo, 3-CN-5-F-fenilo, 3-F-4-$CONH_2$-fenilo, 3-CO_2H-4-CN-fenilo, 3-NMe_2-4-CN-fenilo, 3-Ph-4-$CONH_2$-fenilo, 4-(2-oxo-1-piperidino)-fenilo, tiazol-2-ilo, 4-CO_2Me-tiazol-2-ilo, 4-$CONH_2$-tiazol-2-ilo, 1-Bn-piazol-4-ilo, 5-Ph-oxazol-2-ilo, 5-$CONH_2$-tien-2-ilo, 5-CO_2H-tien-2-ilo, pirid-2-ilo, pirid-3-ilo, pirid-4-ilo, 6-NH_2-Pirid-3-ilo, benzimidazol-2-ilo, 1-Me-benzimidazol-2-ilo, benzoxazol-2-ilo, benzotiazol-2-ilo, 3-NH_2-benzisoxazol-6-ilo, 3-NH_2-benzisoxazol-5-ilo, indazol-5-ilo, indazol-6-ilo, 3-NH_2-indazol-5-ilo, 3-OH-indazol-5-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-4-F-indazol-6-ilo, 3-NH_2-5-F-indazol-6-ilo, 3-NH_2-7-F-indazol-6-ilo, 4-imino-3,4-dihdiro-2H-ftalazin-1-on-7-ilo, 3-(5-tetrazolil)-fenilo, 2,3d-dihidro-isoindol-1-on-6-ilo, quinolin-5-ilo, quinolin-6-ilo, quinolin-8-ilo, isoquinolin-5-ilo, 2H-isoquinolin-1-on-6-ilo, 2,4-diaminoquinazolin-7-ilo, o 4-NH_2-quinazolin-7-ilo;

R^4 es H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, fenilo, 3-F-

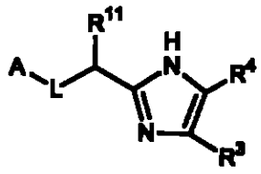
4-CN-fenilo, o 3-NH_2-6-indazolilo; y

R^{11} es Me, neopentilo, ciclohexilmetilo, -$CH_2CH_2CONHBn$, -$CH_2CH_2CONH(CH_2CH_2Ph)$, -$CH_2CH_2CON(Me)Bn$, bencilo, fenetilo, 2-Me-bencilo, 3-Me-bencilo, 4-Me-bencilo, 2-F-bencilo, 3-F-bencilo, 4-F-bencilo, 2-Cl-bencilo, 3-Cl-bencilo, 4-Cl-bencilo, 2-Br-bencilo, 3-Br-bencilo, 4-Br-bencilo, 3-CF_3-bencilo, 4-CF_3-bencilo, 2-NH_2-bencilo, 3-NH_2-bencilo, 2-NO_2-bencilo, 3-NO_2-bencilo, 4-NO_2-bencilo, 3-OMe-bencilo, 4-OMe-bencilo, 3-OCF_2H-bencilo, 2-OCF_3-bencilo, 3-OCF_3-bencilo, 2-OPh-bencilo, 3-OPh-bencilo, 2-OBn-bencilo, 3-OBn-bencilo, 4-OBn-bencilo, 4-COPh-bencilo, 3-CO_2H-bencilo, 3-CO_2Me-bencilo, 3-NHAc-bencilo, 2-NHCOPh-bencilo, 2-NHCOBn-bencilo, 3-NHCOBn-bencilo, 3-N(Me)COPh-bencilo, 3-(-$NHCOCH_2CH_2Ph$)-bencilo, 2-$NHSO_2Ph$-bencilo, 3-$NHSO_2Ph$-bencilo, 3-[$SO_2N(Me)Ph$)-bencilo, 3-[$N(Me)SO_2Ph$)-bencilo, 3-[CONH(*i*-Bu)]-bencilo, 3-[CONH(*t*-Bu)]-bencilo, 3-[CONH(isopentil)]-bencilo, 3-[CONH(2-Me-Ph)]-bencilo, 3-[CONH(3-Me-Ph)]-bencilo, 3-[CONH(4-Me-Ph)]-bencilo, 3-[CONH(4-F-Ph)]-bencilo, 3-[CONH(1-naftil)]-bencilo, 3-(CONHBn)-bencilo, 3-[CONH(4-Cl-Bn)]-bencilo, 3-[CONH(4-OMe-Bn)]-bencilo, 3-[$CONHCH_2CH_2Ph$]-bencilo, 3-[CONH CH_2CH_2(4-OMe-Ph)]-bencilo, 3-[$CONHCH_2CH_2$(2-Cl-Ph)]-bencilo, 3-[$CONHCH_2CH_2$(3-Cl-Ph)]-bencilo, 3-[$CONHCH_2CH_2$(4-Cl-Ph)]-bencilo, 3-[$CONH(CH_2)_3Ph$]-bencilo, 3-[$CONMe_2$]-bencilo, 3-[CON(Me)(Et)]-bencilo, 3-[CON(Me)(*i*-Pr)]-bencilo, 3-

[CON(Me)(*i*-Bu)]-bencilo, 3-[CON(Me)Ph]-bencilo, 3-[CON(Me)(3-Me-Ph)]-bencilo, 3-[CON(Me)(4-Me-Ph)]-bencilo, 3-[CON(Me)Bn]-bencilo, 3-[CON(Me)(3-Cl-Bn)]-bencilo, 3-[CON(Me)(4-Cl-Bn)]-bencilo, 3-[CON(Me)(CH_2CH_2Ph)]-bencilo, 3-[CON(Et)Ph]-bencilo, 3-[CO(1-piperidino)]-bencilo, 3-[CO(4-Ph-1-piperidino)]-bencilo, 3-[CO(1,2,3,4-tetrahidroisoquinolino)]-bencilo, 2-Ph-bencilo, 3-Ph-bencilo, 4-Ph-bencilo, 3-fenetil-bencilo, -CH_2OBn, -CH_2SBn, 1-naftilmetilo, 2-naftilmetilo, tiazol-4-ilmetilo, pirid-2-ilmetilo, pirid-3-ilmetilo, pirid-4-ilmetilo, 1-Bn-imidazol-4-ilmetilo, benzotiazol-2-ilmetilo,



6. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de la Fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, en donde:

R^3 es 3-NH_2-indazol-5-ilo, 3-OH-indazol-5-ilo, 3-NH_2-benzisoxazol-6-ilo, 3-NH_2-benzisoxazol-5-ilo, indazol-5-ilo, indazol-6-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-4-F-indazol-6-ilo, 3-NH2-5-F-indazol-6-ilo, 3-NH_2-7-F-indazol-6-ilo, isoquinolin-5-ilo, quinolin-5-ilo, quinolin-8-ilo, 2H-isoquinolin-1-on-6-ilo, 2,4-diaminoquinazolin-7-ilo, o 4-NH_2-quinazolin-7-ilo.

7. Un compuesto de conformidad con la reivindicación 6, caracterizado porque:

L es $-C(O)NR^{10}-$ o $-NR^{10}C(O)-$;

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t-Bu)$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, -NHEt, $-NHCO_2(t-Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, $-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con

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0-3 R^{4b};

R^{10} es, independientemente cada que se presenta, H, Me, bencilo, fenetilo, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, o $-CH_2CH_2CONHCH_2CH_2Ph$;

R^{11} es alquilo C_1-C_6, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$ cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-2 R^{11b}; y

R^{11b} es, independientemente cada que se presenta, H, F, Cl, Br, CF_3, OMe, OEt, O(i-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-N^8CO_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, alquilo C_1-C_4-, Ph, o Bn.

8. Un compuesto de conformidad con la reivindicación 7, caracterizado porque:

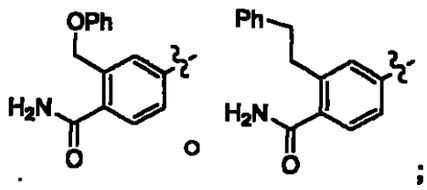
A es substituido con 0-1 R^1 y 0-2 R^2 y son seleccionados de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo; y

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R^{10} es H.

9. Un compuesto de conformidad con la reivindicación 8, caracterizado porque:

A es 4-CH_2NH_2-ciclohexilo, 4-CO_2Me-ciclohexilo, 4-$CONH_2$-ciclohexilo, 4-$NHCO_2$(t-Bu)-ciclohexilo, 4-$NHCO_2$Bn-ciclohexilo, fenilo, 4-Me-fenilo, 3-OMe-fenilo, 4-CH_2NH_2-fenilo, 3-$CONH_2$-fenilo, 4-$CONH_2$-fenilo, 3-amidino-fenilo, 4-amidino-fenilo, 2-F-4-Me-fenilo, 2-Bn-4-CH_2NH_2-fenilo, 4-SO_2NH_2-fenilo, 2-F-5-OMe-fenilo, 2-F-4-Cl-fenilo, 2-F-4-CH_2NH_2-fenilo, 2-F-4-$CONH_2$-fenilo, 2-Cl-4-$CONH_2$-fenilo, 2-Et-4-CH_2NH_2-fenilo, 2-NHEt-4-CH_2NH_2-fenilo, 2-OMe-4-$CONH_2$-fenilo, 3-OMe-4-$CONH_2$-fenilo, 1,2,3,4-tetrahidronaft-2-ilo, 3-Cl-tien-2-ilo, indol-5-ilo, indol-5-ilo, indazol-5-ilo, indazol-6-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-indazol-5-ilo, 1-Me-3-NH_2-indazol-6-ilo, 3-NH_2-benzisoxazol-6-ilo, 1,2,3,4-tetrahidroisoquinolin-6-ilo, 1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-COPh-1,2,3,4-tetrahidroisoquinolin-3-ilo, 2-CO_2Bn-1,2,3,4-tetrahidroisoquinolin-3-ilo, 1,2,3,4-tetrahidroisoquinolin-1-on-6-ilo, 2H-isoquinolin-1-on-6-ilo, isoquinolin-6-ilo, 1-NH_2-isoquinolin-6-ilo, 1-NH_2-3-Me-isoquinolin-6-ilo, 1-NH_2-5,6,7,8-tetrahidroisoquinolin-6-ilo, 4-NH_2-quinazolin-7-ilo, 3H-quinazolin-4-on-7-ilo,



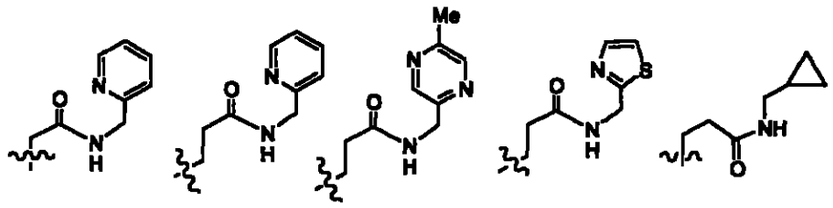
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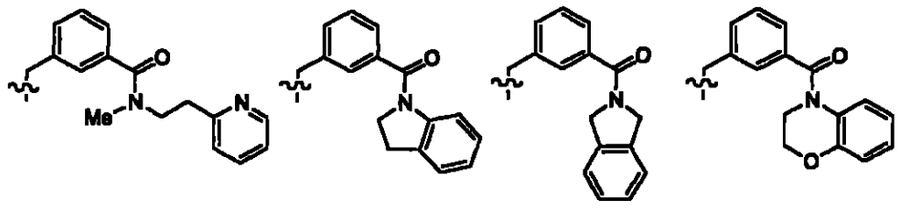
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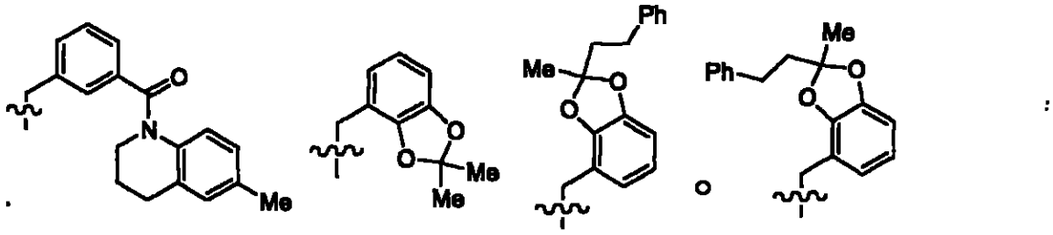
R^4 es H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, fenilo, 3-F-4-CN-fenilo, o 3-NH_{2-6}-indazolilo; y

R^{11} es Me, neopentilo, ciclohexilmetilo, $-CH_2CH_2CONHBn$, $-CH_2CH_2CONH(CH_2CH_2Ph)$, $-CH_2CH_2CON(Me)Bn$, bencilo, fenetilo, 2-Me-bencilo, 3-Me-bencilo, 4-Me-bencilo, 2-F-bencilo, 3-F-bencilo, 4-F-bencilo, 2-Cl-bencilo, 3-Cl-bencilo, 4-Cl-bencilo, 2-Br-bencilo, 3-Br-bencilo, 4-Br-bencilo, 3-CF_3-bencilo, 4-CF_3-bencilo, 2-NH_2-bencilo, 3-NH_2-bencilo, 2-NO_2-bencilo, 3-NO_2-bencilo, 4-NO_2-bencilo, 3-OMe-bencilo, 4-OMe-bencilo, 3-OCF_2H-bencilo, 2-OCF_3-bencilo, 3-OCF_3-bencilo, 2-OPh-bencilo, 3-OPh-bencilo, 2-OBn-bencilo, 3-OBn-bencilo, 4-OBn-bencilo, 4-COPh-bencilo, 3-CO_2H-bencilo, 3-CO_2Me-bencilo, 3-NHAc-bencilo, 2-NHCOPh-bencilo, 2-NHCOBn-bencilo, 3-NHCOBn-bencilo, 3-N(Me)COPh-bencilo, 3-(-$NHCOCH_2CH_2Ph$)-bencilo, 2-$NHSO_2Ph$-bencilo, 3-$NHSO_2Ph$-bencilo, 3-[$SO_2N(Me)Ph$]-bencilo, 3-[$N(Me)SO_2Ph$]-bencilo, 3-[CONH(*i*-Bu)]-bencilo, 3-[CONH(*t*-Bu)]-bencilo, 3-[CONH(isopentil)]-bencilo, 3-[CONH(2-Me-Ph)]-bencilo, 3-[CONH(3-Me-Ph)]-bencilo, 3-[CONH(4-Me-Ph)]-bencilo, 3-[CONH(4-F-Ph)]-bencilo, 3-[CONH(1-naftil)]-bencilo, 3-(CONHBn)-bencilo, 3-[CONH(4-Cl-Bn)]-bencilo, 3-[CONH(4-OMe-Bn)]-bencilo, 3-[$CONHCH_2CH_2Ph$]-bencilo, 3-[$CONHCH_2CH_2(4-OMe-Ph)$]-bencilo, 3-[$CONHCH_2CH_2(2-Cl-Ph)$]-bencilo, 3-[$CONHCH_2CH_2(3-Cl-Ph)$]-bencilo, 3-[$CONHCH_2CH_2(4-Cl-Ph)$]-bencilo, 3-[$CONH(CH_2)_3Ph$]-bencilo, 3-[$CONMe_2$]-bencilo, 3-[CON(Me)(Et)]-bencilo, 3-[CON(Me)(*i*-Pr)]-bencilo, 3-

[CON(Me)(*i*-Bu)]-bencilo, 3-[CON(Me)Ph]-bencilo, 3-[CON(Me)(3-Me-Ph)]-bencilo, 3-[CON(Me)(4-Me-Ph)]-bencilo, 3-[CON(Me)Bn]-bencilo, 3-[CON(Me)(3-Cl-Bn)]-bencilo, 3-[CON(Me)(4-Cl-Bn)]-bencilo, 3-[CON(Me)(CH_2CH_2Ph)]-bencilo, 3-[CON(Et)Ph]-bencilo, 3-[CO(1-piperidino)]-bencilo, 3-[CO(4-Ph-1-piperidino)]-bencilo, 3-[CO(1,2,3,4-tetrahidroisoquinolino)]-bencilo, 2-Ph-bencilo, 3-Ph-bencilo, 4-Ph-bencilo, 3-fenetil-bencilo, -CH_2OBn, -CH_2SBn, 1-naftilmetilo, 2-naftilmetilo, tiazol-4-ilmetilo, pirid-2-ilmetilo, pirid-3-ilmetilo, pirid-4-ilmetilo, 1-Bn-imidazol-4-ilmetilo, benzotiazol-2-ilmetilo,







10. Un compuesto de conformidad con la reivindicación 8, caracterizado porque:

A es 4-CH_2NH_2-ciclohexilo, 4-$NHCO_2$(t-Bu)-ciclohexilo, 4-

$NHCO_2Bn$-ciclohexilo, o 1-NH_2-5,6,7,8-tetrahidroisoquinolin-6-ilo;

L es -C(O)NH- o NHC(O)-;

R^3 es indazol-5-ilo, indazol-6-ilo, 3-NH_2-indazol-5-ilo, 3-OH-indazol-5-ilo, 3-NH_2-indazol-6-ilo, 3-NH_2-4-F-indazol-6-ilo, 3-NH_2-5-F-indazol-6-ilo, 3-NH_2-7-F-indazol-6-ilo, o 4-NH_2-quinazolin-7-ilo;

R^4 es H, Me, F, Br, Cl, o CF_3; y

R^{11} es bencilo substituido con 0-2 R^{11b}.

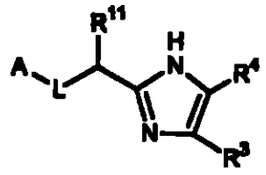
11. Un compuesto de conformidad con la reivindicación 10, caracterizado porque:

A es 4-CH_2NH_2-ciclohexilo;

L es -C(O)NH-; y

R^3 es 3-NH_2-indazol-6-ilo o 4-NH_2-quinazolin-7-ilo.

12. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de la Fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, en donde:

A es substituido con 0-2 R^1 y 0-1 R^2 y seleccionados de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo,

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isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

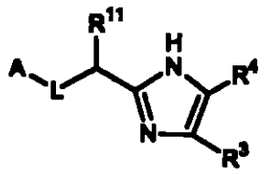
L es $-C(O)NR^{10}-$ o $-NR^{10}C(O)-$;

R^3 es $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, OMe, NH_2, CF_3, CO_2H, CO_2Me, CO_2Et, $-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b}; y

R^{11} es bencilo substituido con 0-2 R^{11b}.

13. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de la Fórmula (II):



(II)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, en donde:

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A está substituido con 0-1 R^1 y 0-2 R^2 y se selecciona de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

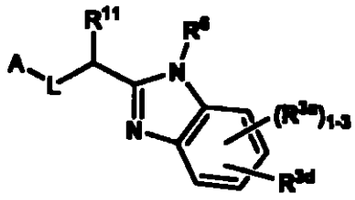
L es $-C(O)NR^{10}-$ o $-NR^{10}C(O)-$;

R^3 es $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es, independientemente cada que se presenta, H, Me, Br, Cl, CF_3, CO_2H, CO_2Me, CO_2Et, fenilo, 3-F-4-CN-fenilo, o 3-NH_2-6-indazolilo; y

R^{11} es bencilo substituido con 0-2 R^{11b}.

14. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de la Fórmula (III):



(III)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, en donde:

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, Me, CN, OH, NH_2, OMe, O(t-Bu), OBn, CF_3, CO_2H, CO_2Me, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, -NHCOMe, $-CONH_2$, $-CH_2CONH_2$, -CONHMe, $-CONMe_2$, $-C(=NH)NH_2$, $-NR^7R^8$, $-SO_2Me$, $-SO_2NH_2$, Ph, o 2-oxo-piperidin-1-ilo;

R^{3d} es H o alquilo C_{1-4};

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprenden: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_r-CONR^8R^9$, alquilo C_{1-6} substituido con 0-2 R^{11a}, alquenilo C_{2-6} substituido con 0-2 R^{11a}, alquinilo C_{2-6} substituido con 0-2 R^{11a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b}.

15. Un compuesto de conformidad con la reivindicación 14, caracterizado porque:

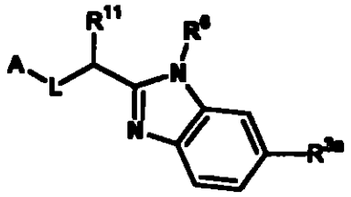
R^1 es, independientemente cada que se presenta, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH(Me)NH_2$, $-C(Me)_2NH_2$, o $-CH_2CH_2NH_2$;

R^{10} es H, Me, bencilo, o fenetilo; y

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R^{11} es Me, $-(CH_2)_r$-fenilo substituido con 0-1 R^{11b}, o $-(CH_2)_r$-heteroarilo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-1 R^{11b}.

16. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de la Fórmula (IV):



(IV)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, en donde:

A es ciclohexilo substituido con 1 R^1, fenilo substituido con 1 R^1, piridilo substituido con 1 R^1, naftilo substituido con 1 R^1, benzisoxazol substituido con 1 R^1, o isoquinolinilo substituido con 0-1 R^1;

L es $-C(O)NH-$, $-C(O)NMe-$, $-C(O)N(bencilo)-$, $-C(O)N(fenetilo)-$, $-NHC(O)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-C(O)NHCH_2-$, o $-NHC(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, o $-CH_2NH_2$;

R^{3a} es F, Cl, Br, Me, CN, OMe, CF_3, CO_2H, CO_2Me, CO_2Et, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2CO_2Et$, $CONH_2$, $-CONHMe$, $-CON(Me)_2$, $-CH_2CONH_2$, o $-C(=NH)NH_2$;

R^6 es H;

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R^{10} es H, Me, bencilo, o fenetilo; y

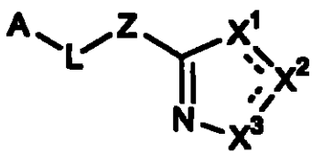
R^{11} es Me, $-(CH_2)r$-fenilo substituido con 0-1 R^{11b}, o $-(CH_2)_r$-heteroarilo de 5-10 miembros substituidos con 0-1 R^{11b} y se selecciona de tiazolilo, imidazolilo, piridilo, y benzotiazolilo.

17. Un compuesto de conformidad con la reivindicación 16, caracterizado porque:

A es 4-CH_2NH_2-ciclohexilo o 4-amidino-fenilo; y

R^{3a} es, independientemente cada que se presenta, CO_2H, CO_2Me, $-CH_2CO_2H$, $-CH_2CO_2Et$, $-CONH_2$, o $-CH_2CONH_2$.

18. Un compuesto de la fórmula (V):



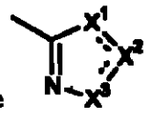
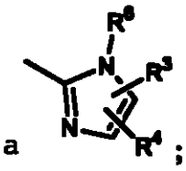
(V)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables del mismo, caracterizado porque:

A es carbociclo C_{3-10} substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo está substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no esta unido a L por medio de cualquiera de los átomos de nitrógeno en el anillo A;

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X^1, X^2 y X^3 son cada uno independientemente CR^3, CR^4, CR^4CR^5, O, $S(O)_p$ N, NR^3, NR^6 o C(O); con la condición de que ningún enlace S-S, S-O, o O-O está presente en el anillo;

con la condición de que  es diferente a  ;

Z es $-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-(CH_2)-$, $-NR^{13}-$, o $-NR^{13}CH_2-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, $-NR^{10}C(O)CH_2-$, $-S(O)_2NR^{10}-$, $-NR^{10}S(O)_2-$, $-CH_2S(O)_2NR^{10}-$, $-CH_2NR^{10}S(O)_2-$, $-S(O)_2NR^{10}CH_2-$, $-NR^{10}S(O)_2CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2NR^7-$, $-NR^7CH_2-$, $-CH_2CH_2NR^7-$, $-NR^7CH_2CH_2$, $-CH_2NR^7CH_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S(O)_p-$, $-S(O)_pCH_2-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2S(O)_p-$, $-S(O)_pCH_2CH_2-$, $-CH_2S(O)_pCH_2-$, $-CH_2C(O)$, $-CH_2C(O)CH_2-$, $-CH_2CH_2C(O)-$, $-C(O)CH_2CH_2-$, o $-C(O)CH_2-$;

R^1 es, independientemente cada que se presenta, $-NH_2$, $-NH$(alquilo C_{1-3}), $-N$(alquilo $C_{1-3})_2$, $-C(=NH)NH_2$, $-C(O)NR^8R^9$, $-S(O)_pNR^8R^9$, $-(CH^2)_rNR^7R^8$, $-(CH_2)_rNR^7C(O)OR^a$, $-CH_2NH_2$, $-CH_2NH$(alquilo C_{1-3}), $-CH_2N$(alquilo $C_{1-3})_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH$(alquilo C_{1-3}), $-CH_2CH_2N$(alquilo $C_{1-3})_2$, $-CH$(alquilo $C_{1-4})NH_2$, $-C$(alquilo $C_{1-4})_2NH_2$, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $=NR^8$, $-NR^8CR^8(=NR^{8a})$, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_rOR^a$, $-(CH_2)_rSR^a$, CN, 1-NH_2-1-ciclopropilo, o alquilo C_{1-6} substituido con 0-1 R^{1a};

R^{1a} es H, $-C(=NR^{8a})NR^7R^8$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CH(=NR^{8a})$, $-NR^7R^8$, $-C(O)NR^8R^9$, F, OCF_3, CF_3, OR^a, SR^a, CN, $-NR^9SO_2NR^8R^9$, -

$NR^8SO_2R^C$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^2 es, independientemente cada que se presenta, H, =O, F, CI, Br, I, OCF_3, CF_3, CHF_2, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{2a}, alquenilo C_{2-6} substituido con 0-2 R^{2a}, alquinilo C_{2-6} substituido con 0-2 R^{2a}, $-(CH_2)$r-carbociclo C_{3-10} substituido con 0-3 R^{2b}, o $-(CH_2)_r$- heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{2b};

R^{2a} es, independientemente cada que se presenta, H, F, CI, Br, I, =O, $=NR^8$, CN, OCF_3, CF_3, OR^a, SR^a, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{2b} es, independientemente cada que se presenta, H, F, Cl, Br, I, =O, $=NR^8$, CN, NO_2, OR^a, SR^a, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^C$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

alternativamente, cuando los grupos R^1 y R^2 son substituidos en atomos en el anillo adyacente, estos pueden tomarse juntos con los átomos en el anillo al cual se enlazan para formar un carbociclo o heterociclo de 5 hasta 7 miembros

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que comprende: átomos de carbono y 0-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el carbociclo o heterociclo es substituido con 0-2 R^{2b};

R^3 es, independientemente cada que se presenta, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r-$ carbociclo C_{3-10} substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^{3a} es, independientemente cada que se presenta, =O, F, Cl, Br, I, OCF_3, CF_3, NO_2, CN, $-(CH_2)_rOR^{3b}$, $-(CH_2)_rSR^{3b}$, $-(CH_2)_rNR^7R^8$, $C(=NR^{8a})NR^8R^9$, $-NHC(=NR^{8a})NR^7R^8$, $-NR^8CR^8(=NR^{8a})$, $-(CH_2)_rNR^8C(O)R^{3b}$, $=NR^8$, $-(CH_2)_rNR^8C(O)R^{3b}$, $-(CH_2)_rNR^8C(O)_2R^{3b}$, $-(CH_2)_rS(O)_pNR^8R^9$, $-(CH_2)_rNR^8S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-S(O)_pR^{3c}$, $-C(O)-$alquilo C_{1-4}, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rOC(O)NR^8R^9$, $-NHCOCF_3$, $-NHSO_2CF_3$, $-SO_2NHR^{3b}$, $-SO_2NHCOR^{3c}$, $-SO_2NHCO_2R^{3c}$, $-CONHSO_2R^{3c}$, $-NHSO_2R^{3c}$, $-CONHOR^{3b}$, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, alquilo C_{1-6} substituido por R^{3d}, alquenilo C_{2-6} substituido por R^{3d}, alquinilo C_{2-6} substituido por R^{3d}, cicloalquilo C_{3-6} substituido por 0-1 R^{3d}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

alternativamente, cuando dos grupos R^{3a} se localizan en

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átomos adyacentes, se toman junto con los átomos a los cuales se enlazan para formar un carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3d};

R^{3b} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3c} es, independientemente cada que se presenta, alquilo C_{1-6} substituido con 0-2 R^{3d}, alquenilo C_{2-6} substituido con 0-2 R^{3d}, alquinilo C_{2-6} substituido con 0-2 R^{3d}, $-(CH_2)_r$ carbocilo C_{3-10} substituido con 0-3 R^{3d}, o $-(CH_2)_r-$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3d};

R^{3d} es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^a$, F, Cl, Br, CN, NO_2, $-(CH_2)_rNR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7C(O)R^b$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2R^C$, $-S(O)_pR^C$, $-(CF_2)_rCF^3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, alquinilo C_{2-6} substituido con 0-2 R^e, $-(CH_2)_r$ carbociclo C_{3-10} substituido

con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^4 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{4b}, o $-(CH_2)_r$ heterociclo 5 de 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^{4a} es, independientemente cada que se presenta, H, F, =O, alquilo C_{1-6}, OR^a, SR^a, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{4b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^C$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

alternativamente, cuando los grupos R^3 y R^4 se localizan en átomos adyacentes, pueden tomarse juntos para formar un

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carbociclo C_{3-10} substituido con 0-2 R^{3d} o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3d};

R^5 es, independientemente cada que se presenta, H, F, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{5a}, alquenilo C_{2-6} substituido con 0-2 R^{5a}, alquinilo C_{2-6} substituido con 0-2 R^{5a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^{5b}, o $-(CH_2)_r$ heterociclo 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{5b};

R^{5a} es, independientemente cada que se presenta, H, =O, OR^a, SR^a, F, Cl, Br, I, CF_3, OCF_3, CN, NO_2, $-NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^C$, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{5b} es, independientemente cada que se presenta, H, =O, $=NR^8$, F, Cl, Br, I, OR^a, SR^a, CN, NO_2, CF_3, $-SO_2R^C$, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_2NR^8R^9$, $-S(O)_2R^C$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, o haloalcoxi C_{1-4};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, haloalquilo C_{1-4}, $-CH_2OR^a$, $-C(O)R^C$, $-C(O)_2R^C$, $-S(O)_2R^C$, o $-(CH_2)_r$ fenilo substituido con 0-3 R^d;

R^7 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n$-carbociclo C_{3-10}, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, -CHO, $-C(O)_2R^c$, $-S(O)_2R^c$, $-CONR^8R^c$, $-OCONHR^c$, $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(alquilo C_{1-4}), o $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(arilo C_{6-10}); en donde el alquilo, carbociclo, heteroarilo, y arilo son opcionalmente substituidos con 0-2 R^f;

R^8 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo, o $-(CH_2)_n$- heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde el alquilo, fenilo y heterociclo son opcionalmente substituidos con 0-2 R^f;

alternativamente, R^7 y R^8, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d;

R^{8a} es, independientemente cada que se presenta, H, OH, alquilo C_{1-6}, alcoxi C_{1-4}, (arilo C_{6-10})-alcoxi C_{1-4}, $-(CH_2)_n$-fenilo, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)_2R^c$, $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(alquilo C_{1-4}), o $-C(O)O$-(alquilo C_{1-4})$OC(O)$-(arilo C_{6-10}); en donde el fenilo, arilo, y heteroarilo es opcionalmente substituido con 0-2 R^f;

R^9 es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo; en donde el alquilo y fenilo

son opcionalmente substituidos con 0-2 R^f;

R^{9a} es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

alternativamente, R^8 y R^9, cuando se enlazan al mismo nitrógeno, se combinan para formar un anillo heterocíclico de 5 hasta 10 miembros que comprende átomos de carbono y 0-2 heteroátomos adicionales seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3R^{10a}, alquenilo C_{2-6} substituido con 0-3 R^{10a}, alquinilo C_{2-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$- heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^{10a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, SR^a, F, CF_3, CN, NO_2, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8SO_2R^C$-, $-S(O)R^C$, o $-S(O)_2R^C$;

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CR^{14}R^{15})_r$- carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CR^{14}R^{15})_r$- heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en

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donde el heterociclo es substituido con 0-3 R^{11b};

R^{11a} es, independientemente cada que se presenta, H, =O, alquilo C_{1-4}, OR^a, CF_3, SR^a, F, CN, NO_2, NR^7R^8, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-C(O)R^a$, $-C(O)OR^a$, $-S(O)_pR^C$, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4} $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^d;

R^{11b} es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, CN, NO_2, CF_3, OCF_3, $OCHF_2$, $-C(O)R^a$, $-C(O)OR^a$, $-SOR^C$, $-SO_2R^C$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^C$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, cicloalquilo C_{3-6}, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r-$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales se enlazan para formar un heterociclo de 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-2 R^g;

R^{12} es, independientemente cada que se presenta, H, F, o

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alquilo C_{1-4};

R^{13} es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-(CH_2)_n$-fenilo, $-(CH_2)_n$-(heteroarilo de 5-10 miembros), $-C(O)R^c$, $-C(O)OR^c$, $-CONR^aR^c$, $-OCONR^aR^c$, $-S(O)_2R^c$, $-C(O)O-$(alquilo C_{1-4})$-OC(O)-$(alquilo C_{1-4}), o $-C(O)O-$(alquilo C_{1-4})$-OC(O)-$(arilo C_{6-10}); en donde el alquilo, fenilo, heteroarilo, arilo son opcionalmente substituidos con 0-2 R^f;

R^{14} y R^{15} son, independientemente cada que se presenta, H, F, o alquilo C_{1-4};

alternativamente, R^{14} se combina con R^{15} para formar =O;

R^a es, independientemente cada que se presenta, H, CF_3, alquilo C_{1-6}, $-(CH_2)_r-$ cicloalquilo C_{3-7}, $-(CH_2)_r$ arilo C_{6-10}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$; en donde los grupos cicloalquilo, arilo y heteroarilo son opcionalmente substituidos con 0-2 R^f.

R^b es, independientemente cada que se presenta, CF_3, OH, alcoxi C_{1-4}, alquilo C_{1-6}, $-(CH_2)_r$ carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$ heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d;

R^c es, independientemente cada que se presenta, CF_3, alquilo C_{1-6} substituido con 0-2 R^f, cicloalquilo C_{3-6} substituido con 0-2 R^f, arilo C_{6-10}, heteroarilo de 5 hasta 10

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miembros, (arilo C_{6-10})-alquilo C_{1-4}, o (heteroarilo de 5 hasta 10 miembros)-alquilo C_{1-4}, en donde los grupos arilo y heteroarilo son opcionalmente substituidos con 0-3 R^f;

R^d es, independientemente cada que se presenta, H, =O, $=NR^8$, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^7R^8$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6} substituido con 0-2 R^e, alquenilo C_{2-6} substituido con 0-2 R^e, o alquinilo C_{2-6} substituido con 0-2 R^e;

R^e es, independientemente cada que se presenta, =O, OR^a, F, Cl, Br, I, CN, NO_2, $-NR^8R^9$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-NR^8C(O)R^a$, $-C(O)NR^7R^8$, $-SO_2NR^8R^9$, $NR^8SO_2NR^8R^9$, $-NR^8SO_2$-alquilo C_{1-4}, $-NR^8SO_2CF_3$, $-NR^8SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, o $-(CF_2)_rCF_3$;

R^f es, independientemente cada que se presenta, H, =O, $-(CH_2)_rOR^g$, F, Cl, Br, I, CN, NO_2, $-NR^{9a}R^{9a}$, $-C(O)R^g$, $-C(O)OR^g$, $-NR^{9a}C(O)R^g$, $-C(O)NR^{9a}R^{9a}$, $-SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2NR^{9a}R^{9a}$, $-NR^{9a}SO_2$-alquilo C_{1-4}, $-NR^{9a}SO_2CF_3$, $-NR^{9a}SO_2$-fenilo, $-S(O)_2CF_3$, $-S(O)_p$-alquilo C_{1-4}, $-S(O)_p$-fenilo, $-(CF_2)_rCF_3$, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, o $-(CH_2)_n$-fenilo;

R^g es, independientemente cada que se presenta, H, alquilo C_{1-6}, o $-(CH_2)_n$-fenilo;

n, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4;

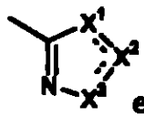
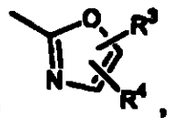
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p, cada que se presenta, se selecciona de 0, 1, y 2;

r, cada que se presenta, se selecciona de 0, 1, 2, 3, y 4; y

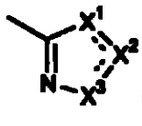
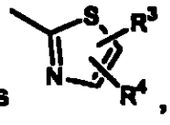
s, cada que se presenta, se selecciona de 1, 2, 3, y 4;

con la condición de que:

(a). cuando el grupo  es  ,

i. y cuando L es -NHC(O)-, R^{14} no se combina con R^{15} para formar =O;

ii. y cuando L es -C(O)NH- y A es fenilo, R^1 no es -NHC(O)H;

(b). cuando el grupo  es  ,

i. y cuando L es -NHC(O)- y R^3 se combina con R^4 para formar un anillo fenilo fusionado con el tiazol, el enillo fenilo es subsituido con al menos un R^{3a};

ii. y cuando L es -C(O)NH- y A es fenilo, R^1 no es -NHC(O)H; y

(c). A no es oxazolinona, tiofeno, oxadiazol o furano substituidos o no substituidos.

19. Un compuesto de conformidad con la reivindicación 18, caracterizado porque:

A es cicloalquilo C_{3-8} substituido con 0-1 R^1 y 0-3 R^2, cicloalquenilo C_{4-8} substituido con 0-1 R^1 y 0-3 R^2, fenilo

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substituido con 0-1 R^1 y 0-3 R^2, naftilo substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no es unido a L por medio de los átomos de nitrógeno en el anillo A;

Z es $-C(R^{11})(R^{12})-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$, $-C(O)NR^{10}CH_2-$, o $-NR^{10}C(O)CH_2-$;

R^3 es, independientemente cada que se presenta, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-cicloalquilo C_{3-8} substituido con 0-2 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^4 es H, F, Cl, Br, I, OCF_3, CF_3, OR^a, SR^a, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un

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heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{4b};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6} substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$-heterociclo de 5 hasta 10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b}.

20. Un compuesto de conformidad con la reivindicación 18, caracterizado porque:

A es cicloalquilo C_{5-6} substituido con 0-1 R^1 y 0-2 R^2, cicloalquenilo C_{5-6} substituido con 0-1 R^1 y 0-2 R^2, fenilo substituido con 0-1 R^1 y 0-3 R^2, naftilo substituido con 0-1 R^1 y 0-3 R^2, o un heterociclo de 5 hasta 10 miembros que

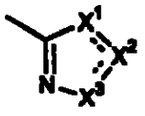
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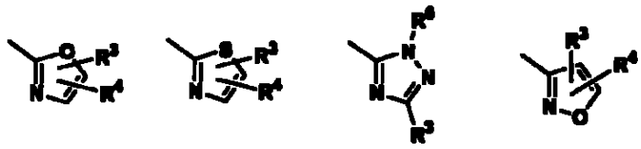
comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-1 R^1 y 0-3 R^2; con la condición de que cuando A es un heterociclo que contiene uno o más átomos de nitrógeno, A no es unido a L por medio a cualquiera de los átomos de nitrógeno en el anillo A;

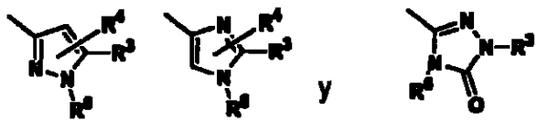
R^3 es, independientemente cada que se presenta, $-(CH_2)_r-C(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d}; y

R^6 es, independientemente cada que se presenta, H o alquilo C_{1-6}.

21. Un compuesto de conformidad con la reivindicación 18, caracterizado porque:

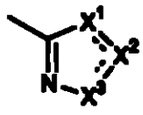
el grupo  se selecciona de:

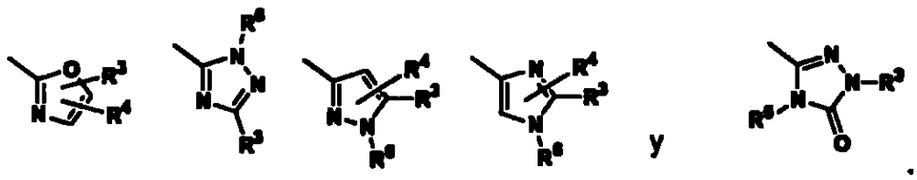




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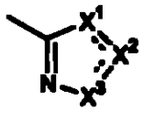
22. Un compuesto de conformidad con la reivindicación 18, caracterizado porque:

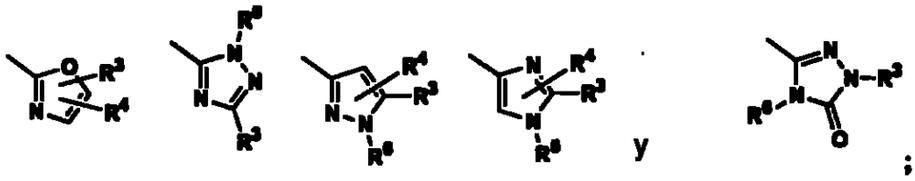
el grupo  se selecciona de:



23. Un compuesto de conformidad con la reivindicación 18, caracterizado porque:

A es substituido con 0-1 R^1 y 0-2 R^2 y seleccionados de: cicloalquilo C_{3-7}, fenilo, naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

el grupo  se selecciona de:



Z es $-CH(R^{12})-$;

L es $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-CH_2C(O)NR^{10}-$, $-CH_2NR^{10}C(O)-$,

$-C(O)NR^{10}CH_2-$, o $-NR^{10}C(O)CH_2-$;

R^3 es, independientemente cada que se presenta, $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_rC(O)NR^8(CH_2)_sCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-indanilo substituido con 0-3 R^{3a} y 0-1 R^{3d} o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y S(O)p, y substituido con 0-3 R^{3a} y 0-1 R^{3d};

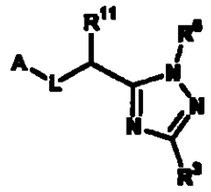
R^4 es, independientemente cada que se presenta, H, =O, F, Cl, Br, I, OCF_3, CF_3, CN, NO_2, $-C(O)R^a$, $-C(O)OR^a$, $-NR^7R^8$, $-C(O)NR^8R^9$, $-NR^7C(O)R^b$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^C$, $-S(O)R^C$, $-S(O)_2R^C$, alquilo C_{1-6} substituido con 0-2 R^{4a}, alquenilo C_{2-6} substituido con 0-2 R^{4a}, alquinilo C_{2-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, y substituido con 0-3 R^{4b};

R^6 es H, alquilo C_{1-6}, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-2 R^{10a}, $-(CH_2)_r$-fenilo substituido con 0-2 R^d, o $-(CH_2)_r$- heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^d; y

R^{12} es, independientemente cada que se presenta, H, F, o Me.

24. Un compuesto de conformidad con la reivindicación 18, caracterizado porque el compuesto es de la Fórmula (VI):



(VI)

o sus estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptable del mismo, en donde:

R^3 es $-(CH_2)_rC(O)NR^8R^9$, $-(CH_2)_sC(O)NR^8(CH^2)_rCO_2R^{3b}$, $-(CH_2)_rCO_2R^{3b}$, $-(CH_2)_r$-fenilo substituido con 0-3 R^{3a} y 0-1 R^{3d}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{3a}, $-(CH_2)_r$-indanilo substituido con 0-2 R^{3a}, o $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{3a} y 0-1 R^{3d};

R^6 es, independientemente cada que se presenta, H, alquilo C_{1-6}, $-CH_2OR^a$, $-C(O)R^c$, $-C(O)_2R^c$, o $-(CH_2)_r$-fenilo substituido con 0-3 R^d;

R^{10} es, independientemente cada que se presenta, H, alquilo C_{1-6} substituido con 0-3 R^{10a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^d, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es

substituido con 0-3 R^d; y

R^{11} es haloalquilo C_{1-4}, $-(CH_2)_rC(O)NR^8R^9$, alquilo C_{1-6} substituido con 0-3 R^{11a}, alquenilo C_{2-6}, substituido con 0-3 R^{11a}, alquinilo C_{2-6} substituido con 0-3 R^{11a}, $-(CH_2)_r$-carbociclo C_{3-10} substituido con 0-3 R^{11b}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-3 R^{11b}.

25. Un compuesto de conformidad con la reivindicación 24, caracterizado porque:

R^1 es, independientemente cada que se presenta, F, Cl, Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t\text{-}Bu)$, $-CH(Me)NH_2$, $-CMe_2NH_2$, $-NHEt$, $-NHCO_2(t\text{-}Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

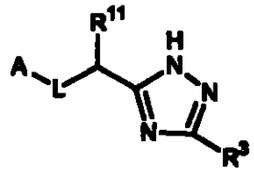
R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, $-(CH_2)_r$fenilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, naftilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, indanilo substituido con 0-2 R^{3a} y 0-1 R^{3d}, o un $-(CH_2)_r$ heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-2 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a} y 0-1 R^{3d};

R^6 es H;

R^{10} es, independientemente cada que se presenta, H, Me, bencilo, fenetilo, $-CH_2CH_2CO_2H$, $-CH_2CH_2CO_2Me$, $-CH_2CH_2CO_2Et$, $-CH_2CH_2CONH_2$, o $-CH_2CH_2CONHCH_2CH_2Ph$; y

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, CH_2SBn, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$-heterociclo de 5-10 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{11b}.

26. Un compuesto de conformidad con la reivindicación 18, caracterizado porque el compuesto es de la Fórmula (VII):



(VII)

o sus estereoisómeros, tautómeros, sales o solvatos del mismo farmacéuticamente aceptable,

A es substituido con 0-2 R^1 y 0-1 R^2 y seleccionado de: cicloalquilo C_{3-7}, fenilo naftilo, 1,2,3,4-tetrahidronaftilo, piridilo, indazolilo, benzimidazolilo, benzisoxazolilo, isoquinolinilo, 5,6,7,8-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, quinazolinilo, 1H-quinazolin-4-onilo, 2H-isoquinolin-1-onilo, 3H-quinazolin-4-onilo, 3,4-dihidro-2H-isoquinolin-1-onilo, 2,3-dihidroisoindolinonilo, y ftalazinilo;

L es $-C(O)NH-$ o $-NHC(O)-$;

R^1 es, independientemente cada que se presenta, F, Cl,

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Me, Et, $-NH_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2Bn$, $-CH_2NHCO_2(t-Bu)$, $-CH(Me)NH_2$, $-CMe_2NH_2$, -NHEt, $-NHCO_2(t-Bu)$, $-NHCO_2Bn$, $-SO_2NH_2$, OR^a, o $-CH_2R^{1a}$;

R^3 es $-CO_2H$, $-CO_2Me$, $-C(O)NHCH_2CO_2H$, $-C(O)NHCH_2CO_2Et$, $-C(O)NH_2$, $-C(O)NHMe$, $-C(O)NHBn$, fenilo substituido con 0-2 R^{3a}, naftilo substituido con 0-2 R^{3a}, indanilo substituido con 0-2 R^{3a}, o un heterociclo de 5 hasta 10 miembros que comprende: átomos de carbono y 1-2 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{3a};

R^4 es H, F, Cl, Br, CF_3, CO_2H, CO_2Me, CO_2Et, alquilo C_{1-6} substituido con 0-2 R^{4a}, fenilo substituido con 0-2 R^{4b}, o heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en donde el heterociclo es substituido con 0-2 R^{4b};

R^{11} es alquilo C_{1-6}, $-CH_2CONR^8R^9$, $-CH_2CH_2CONR^8R^9$, $-CH_2OBn$, $-CH_2SBn$, $-(CH_2)_r$-cicloalquilo C_{3-7} substituido con 0-2 R^{11b}, $-(CH_2)_r$-fenilo substituido con 0-2 R^{11b}, $-(CH_2)_r$-naftilo substituido con 0-2 R^{11b}, o $-(CH_2)_r$-heteroarilo de 5 hasta 10 miembros substituidos con 0-2 R^{11b} y seleccionados de tiazolilo, oxazolilo, triazolilo, tetrazolilo, imidazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, benzimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, tetrahidroquinolinilo, y tetrahidroisoquinolinilo;

R^{11b} es, independientemente cada que se presenta, H, F,

Cl, Br, CF_3, OMe, OEt, O(i-Pr), OCF_3, $OCHF_2$, CN, OPh, OBn, NO_2, $-NH_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^7R^8$, $-NR^7C(O)R^b$, $-NR^8C(O)_2R^c$, $-S(O)_pNR^8R^9$, $-NR^8S(O)_pR^c$, $-SO_2R^c$, alquilo C_1-C_4-, Ph, o Bn;

alternativamente, cuando dos grupos R^{11b} son substituyentes en átomos adyacentes estos pueden tomarse junto con los átomos a los cuales están enlazados para formar un heterociclo 5 hasta 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ y substituido con 0-2 R^g.

27. Un compuesto de conformidad con la reivindicación 26, caracterizado porque:

A es 4-CH_2NH_2-ciclohexilo o 4-amidino-fenilo; y

R^3 es fenilo, 3-CN-fenilo, 4-CN-fenilo, 3-Br-fenilo, 4-Br-fenilo, 3-OMe-fenilo, 4-OMe-fenilo, 3-CF_3-fenilo, 4-CF_3-fenilo, 3-CO_2H-fenilo, 4-CO_2H-fenilo, 4-CO_2Me-fenilo, 4-CH_2CO_2H-fenilo, 4-CH_2CO_2Me-fenilo, 3-$CONH_2$-fenilo, 4-$CONH_2$-fenilo, 4-CONHMe-fenilo, 4-$CON(Me)_2$-fenilo, 4-CH_2CONH_2-fenilo, 4-amidino-fenilo, o 2,4-diF-fenilo.

28. Un compuesto, caracterizado porque se selecciona de:

(S)-4-carbamimidoil-N-(2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)benzamida,

(S)-4-(aminometil)-N-(2-fenil-1-(4-fenil-1H-imidazol-2-il)etil)-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-{1-[4-(4-ciano-fenil)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

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(S)-4-(aminometil)-N-{1-[4-(4-bromo-fenil)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-{1-[4-(4-metoxi-fenil)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-(1-bencil-1H-imidazol-4-il)-1-(4-fenil-1H-imidazol-2-il)-etil]-trans-ciclohexancarboxamida,

éster de metilo del ácido (S)-3-(2-{1-[trans-(4-aminometil)-ciclohexancarboxamido]-2-fenil-etil}-1H-imidazol-4-il)-benzoico,

(S)-4-(aminometil)-N-{1-[4-(3-fluoro-fenil)-1H-imidazol-2-il]-2--fenil-etil}-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-{1-[4-(3-bromo-fenil)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-(3-clorofenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-{2-(4-clorofenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[1-(4-fenil-1H-imidazol-2-il)-2-(2-piridil)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-fenil-1-(4-tiazol-2-il-1H-imidazol-2--il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-fenil-1-(4-piridin-2-il-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

ácido (S)-[4-(2-{1-[trans-(4-Aminometi)-ciclohexancarboxamido]-2-fenil-etil}-1H-imidazol-4-il)-

fenil]-acético,

(S)-4-(aminometil)-N-{1-[(4-carbamoilmetil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

(S)-[4-(2-{1-[(4-aminometil)-ciclohexancarboxamido]-2-fenil-etil}-1H-imidazol-4-il)]-benzamida,

(S)-[3-(2-{1-[(4-Aminometil)-ciclohexancarboxamido]-2-fenil-etil}-1H-imidazol-4-il)]-benzamida,

(S)-4-(2-(1-trans-(4-aminometil)-ciclohexancarboxamido)-2-feniletil)-1H-imidazol-4-il)-N,N-dimetilbenzamida,

(S)-2-(1-trans-(4-aminometil)-ciclohexancarboxamido)-2-fenil-etil)-1H-benzo[d]imidazol-5-carboxamida,

N-(4-carbamimidoilfenil)-3-fenil-2-(4-fenil-1H-imidazol-2-il)propanamida,

4-(2-(1-(4-carbamimidoilfenilamino)-1-oxo-3-fenilpropan-2-il)-1H-imidazol-4-il)benzamida,

4-(2-(1-(1-aminoisoquinolin-6-ilamino)-1-oxo-3-fenilpropan-2-il)-1H-imidazol-4-il)benzamida,

4-(2-(4-(4-carbamimidoilfenil)-1H-imidazol--2-il)-3-fenilpropanamido)benzamida,

(S)-4-(aminometil)-N-{1-[4-(2,4-difluoro-fenil)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-{1-[4-(4-fluoro-fenil)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

ácido (S)-3-(2-(1-trans-(4-aminometil)-ciclohexancarboxamido)-2-fenil-etil)-1H-imidazol-4-il)-

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benzoico,

(S)-N-(1-(4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il)-2-feniletil)-4-(aminometil)-trans-ciclohexancarboxamida,

4-[2-[1-[4-[4-(carbamimidoilfenil]-1H-imidazol-2-il]-2-fenil-etil]-1H-imidazol-4-il]-benzamida,

(S)-4-(aminometil)-N-[1-(4-fenil-1H-imidazol-2-il)-2-(4-piridinil)etil]-trans-ciclohexancarboxamida,

(S)-4-[2-[1-[4-(aminometil)ciclohexancarboxamido]amino]-2-feniletil]-4-(bromo-1H-imidazol-5-il)-benzamida,

ácido (S)-3-[2-[1-[4-(aminometil) ciclohexancarboxamido]-2-feniletil)-1H-imidazol-4-il]-fenilacético,

(S)-3-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-fenil-etil]-1H-imidazol-4-il]-fenilacetamida,

(S)-4-(aminometil)-N-[1-[4-(3-hidroxifenil)-1H-imidazol-2-il]-2-feniletil]-trans-ciclohexancarboxamida,

éster de etilo del ácido (S)-3-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-fenil-etil]-1H-imidazol-4-il]-fenil-acético

2-[4-(4-carbamimidoil-fenil)-1H-imidazol-2-il]-3,N-difenil-propionamida,

(S)-4-(aminometil)-N-[2-(4-fluorofenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-[4-(benciloxi)fenil]-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-(4-benzoilfenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[1-(4-fenil-1H-imidazol-2-il)-2-[3-(trifluorometil)fenil]etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[-2-(3-nitrofenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-(2-clorofenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-(1-naftalenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[2-(2-naftalenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N-[-1-[4,5-bis(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-feniletil]-trans-ciclohexancarboxamida,

(S)-4-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-feniletil]-4-(trifluorometil)-1H-imidazol-5-il]-benzamida,

(S)-N-[1-[4-[4-(carbamimidoil)fenil]-1H-imidazol-2-il]-2-feniletil]-benzamida,

(S)-4-(aminometil-N-[2-(2-bromofenil)-1-(4-fenil-1H-imidazol-2-il)etil]-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-bromo-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-transciclohexancarboxamida,

éster de metilo del ácido (S)-5-[4-(carbamoilfenil]-2-

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[1-[4-(aminometil)ciclohexancarboxamido]-2-feniletil]-1H-imidazol-4-carboxílico,

4-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-[2-(trifluorometoxi)fenil]etil]-1H-imidazol-4-il]-benzamida,

4-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-[2-(difluorometoxi)fenil]etil]-1H-imidazol-4-il]-benzamida,

(S)-N-[1-[4-[4-(carbamoil)fenil]-1H-imidazol-2-il]-2-fenil-etil]-4-(aminometil)-benzamida,

(S)-N-[1-[4-[4-(carbamoil)fenil]-1H-imidazol-2-il]-2-fenil-etil]-4-(aminometil)-2-fluoro-benzamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-benzamida,

(S)-3-amino-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-1H-indazol-6-carboxamida,

(S)-3-amino-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil]-1,2-benzisoxazol-6-carboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-2-fluoro-benzamida,

(S)-N-[1-[4-[4-(carbamimidoil)fenil]-1-(2-fenil-etil)-1H-imidazol-2-il]-2-feniletil]-benzamida,

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(S)-N-{1-[4-[4-(carbamimidoil)fenil]-1-metil-1H-imidazol-2-il]-2-feniletil]-benzamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-2-fluoro-5-metoxi-benzamida,

(S)-4-[2-[(1-[4-(aminometil)ciclohexancarboxamido]-2-fenil-etil]-4-cloro-1H-imidazol-5-il]-benzamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-1,4-bencendicarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(2,2-dimetil-1,3-benzodioxol-4-il)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

4-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-[3-(difluorometoxi)fenil]etil]-1H-imidazol-4-il]-benzamida,

(S)-4-[2-[1-[4-(aminometil)ciclohexancarboxamido]-2-feniletil]-4-fenil-1H-imidazol-5-il]-benzamida,

(S)-1-amino-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-6-isoquinolincarboxamida,

(S)-1-amino-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil]-5,6,7,8-tetrahidro-6-isoquinolincarboxamida,

N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(3-fenoxifenil)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(2-fenoxifenil)etil]-4-(aminometil)-trans-

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ciclohexancarboxamida,

1-amino-N-[(1S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil]-5,6,7,8-tetrahidro-(6S)-6-isoquinolincarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(2-nitrofenil)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[-1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(3-nitrofenil)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(2-aminofenil)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(3-aminofenil)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]--2-[1,1'-bifenil]-2-iletil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[1,1'-bifenil]-3-iletil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-1,2,3,4-tetrahidro-6-isoquinolincarboxamida,

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(S)-N-[1-[4-(3-amino-1H-indazol-6--il)-1H-imidazol-2-il]-2-[3-[(fenilsulfonil)amino]fenil]etil]-4-(aminometil)-trans-ciclohexancarboxamida,

N-[2-(2S)-[2-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-[{trans-[4-(aminometil)ciclohexancarboxamida]etil]fenil]-fenilacetamida,

N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[(2S)-2-metil-2-(2-feniletil)-1,3-benzodioxol-4-il)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[(2R)-2-metil-2-(2-feniletil)-1,3-benzodioxol-4-il]etil)-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-4-(aminometil)-N--[1-[4-(4-amino-7-quinazolinil)-5-cloro-1H-imidazol-2-il]-2-feniletil]-trans-ciclohexancarboxamida,

N-[2-[(2S)-2-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[[[trans-4-(aminometil)ciclohexancarboxamido]etil]-fenil]-bencenpropanamida,

(S)-N-1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[2-[(fenilsulfonil)amino]fenil]etil]-4-(aminometil)-trans-ciclohexancarboxamida,

N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[2-(fenilmetoxi)fenil]etil]-4-(aminometil)-trans-ciclohexancarboxamida,

N-[2-[(2S)-2-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-

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il]-2-[[[trans-4-aminometil)ciclohexancarboxamido]etil]fenil]-benzamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(2-bromofenil)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-3,3-dimetilbutil]-4-(aminometil)-trans-ciclohexancarboxamida,

(R)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-(fenilmetoxi)etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(R)-N-[1-[4-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-2-[(fenilmetil)tio]etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-4-fluoro-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil)-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-N-[1-[4-(3-amino-5-fluoro-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-feniletil]-4-(aminometil)-trans-ciclohexancarboxamida,

éster de metilo del ácido 3-[2-[4-[4-(aminocarbonil)fenil]-1H-imidazol-2-il]-2-[[[trans-4-(aminometil)ciclohexancarboxamido]etil]-benzoico

N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-[3-(difluorometoxi)fenil]etil]-4-(aminometil)-trans-ciclohexancarboxamida,

(S)-3-amino-N-[1-[4-[4-(carbamimidoil)fenil]-1H-imidazol-2-il]-2-feniletil]-1H-indazol-5-carboxamida,

ácido 3-[2-[4-[4-(aminocarbonil)fenil]-1H-imidazol-2-il]-2-[[[trans-4-(aminometil)ciclohexancarboxamido]etil]-benzoico,

(S)-3-Amino-N-{1-[4-(4-carbamimidoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-1H-indazol-6-carboxamida,

(S)-N-{1-[4-(4-carbamimidoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-1H-indazol-6-carboxamida,

(S)-N-{1-[4-(4-carbamimidoil-fenil)-1H-imidazol-2-il]-2-fenil-etil}-1H-indol-6-carboxamida,

(S)-N-{1-[4-(4-carbamimidoil-fenil)-1-etil-1H-imidazol-2-il]-2-fenil-etil}-benzamida,

N^1-{(S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-2-fluoro-tereftalamida,

N^1-{(S)-1-[4-(4-amino-quinazoiin-7-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-2-fiuoro-tereftalamida,

1-amino-N-[(1S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil]-5,6,7,8-tetrahidro-(6R)-6-isoquinolincarboxamida,

(S)-1-amino-N-{1-[4-(4-amino-quinazolin-7-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-5,6,7,8-tetrahidro-isoquinolin-6-carboxamida,

(S)-1-amino-N-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-3-metil-isoquinolin-6-

carboxamida,

4-(2-{1-{(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(piperidin-1-carbonil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(o-tolilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(metil-fenil-carbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(bencilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

(S)-N-{1-[4-(3-amino-7-fluoro-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-4-aminometil-trans-ciclohexancarboxamida,

(S)-N-{1-[4-(3-amino-1H-indazol-5-il)-1H-imidazol-2-il]-2-fenil-etil}-4-aminometil-trans-ciclohexancarboxamida,

(S)-N-{1-[4-(3-hidroxi-1H-indazol-5-il)-1H-imidazol-2-fenil-etil}-4-aminometil-trans-ciclohexancarboxamida,

(S)4-aminometil-N-[1-(4-bifenil-4-il-1H-imidazol-2-il)-2-fenil-etil)-trans-ciclohexancarboxamida,

(S)-4-aminometil-N-[1-(4-benzo[1,3]dioxol-5-il-1H-imidazol-2-il)-2-fenil-etil]-ciclohexancarboxamida,

(S)-4-aminometil-N-[1-(4-naftalen-2-il-1H-imidazol-2-

il)-2-fenil-etil]-trans-ciclohexancarboxamida,

N^4-{(S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-2-metoxi-tereftalamida,

(S)-4-aminometil-N-{1-[4-(3-amino-fenil)-1H-imidazol-2-fenil-etil}-ciclohexancarboxamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-isobutil-carbamoil-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(3-metil-butilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-terc-butilcarbamoil-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(4-cloro-bencilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(4-cloro-bencilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(4-metoxi-bencilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-fenetilcarbamoil-fenil]-etil}-1H-imidazol-4-il)-benzamida,

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4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-[2-(4-cloro-fenil)-etilcarbamoil]-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-[2-(4-metoxi-fenil)-etilcarbamoil]-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(3-fenil-propilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(bencil-metil-carbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(metil-fenetil-carbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-m-tolil-carbamoil-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-p-tolil-carbamoil-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(4-fluoro-fenilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-

[3-(naftalen-1-ilcarbamoil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(4-fenil-piperidin-1-carbonil)-fenil]-etil}-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-trans-ciclohexancarboxamido]-2-[3-(3,4-dihidro-1H-isoquinolin-2-carbonil)-fenil-]-etil}-1H-imidazol-4-il)-benzamida,

(S)-N-[1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-(3-bencensulfonilamino-fenil)-etil]-4-aminometil-tran-ciclohexancarboxamida,

(S)-N-{1-[4-(4-benciloxi-fenil)-1H-imidazol-2-il]-2-fenil-etil}-4-aminometil-trans-ciclohexancarboxamida,

(S)-N-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-1-oxo-1,2-dihidro-isoquinolin-6-carboxamida,

(S)-N-{1-[5-cloro-4-(2,4-diamino-quinazolin-7-il)-1H-imidazol-2-il]-2-fenil-etil}-4-aminometil-trans-ciclohexancarboxamida,

(S)-N-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-3-amino-1H-indazol-5-carboxamida,

4-(2-{(S)-1-[(4-aminometil-trans-ciclohexancarbonil)-amino]-2-fenil-etil}-5-bromo-1H-imidazol-4-il)-2-fluoro-benzamida,

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4-(2-{(S)-1-[(4-aminometil-trans-ciclohexancarbonil)-amino]-2-fenil-etil}-5-cloro-1H-imidazol-4-il)-2-fluoro-benzamida,

(S)-N-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-1-oxo-1,2,3,4-tetrahidro-isoquinolin-6-carboxamida,

(S)-N-[1-(5-metil-4-fenil-1H-imidazol-2-il)-2-fenil-etil]-4-aminometil-trans-ciclohexancarboxamida,

4-(2-{(S)-1-[(4-aminometil-trans-ciclohexancarbonil)-amino]-2-fenil-etil}-5-metil-1H-imidazol-4-il)-benzamida,

(S)-N-{1-[4-(3-amino-1H-indazol-6-il)-5-metil-1H-imidazol-2-il]-2-feniletil}-4-aminometil-trans-ciclohexancarboxamida,

1-amino-N-{(S)-1-[4-(4-carbamoil-fenil)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-5,6,7,8-tetrahidro-isoquinolin-6-carboxamida,

ácido 1-amino-N-{(S)-1-[4-(4-carbamoil-fenil)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-5,6,7,8-tetrahidro-isoquinolin-6-carboxílico,

1-amino-N-{(S)-1-[4-(4-carbamoil-fenil)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-5,6,7,8-tetrahidro-isoquinolin-6-carboxamida,

ácido 1-amino-N-{(S)-1-[4-(4-carbamoil-fenil)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-5,6,7,8-tetrahidro-isoquinolin-6-carboxílico,

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4-aminometil-N-{(S)-1-[4-(6-amino-piridin-3-il)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

4-aminometil-N-{(S)-1-[4-(3-cloro-fenil)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

ácido 5-(2-{(S)-1-[(4-aminometil-ciclohexancarboxamido]-2-fenil-etil}-5-metil-1H-imidazol-4-il)-tiofen-2-carboxílico,

5-(2-{(S)-1-[(4-aminometil-ciclohexancarboxamido]-2-fenil-etil}-5-metil-1H-imidazol-4-il)-tiofen-2-carboxamida,

N^4-{(S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-2-fenoximetil-tereftalamida,

N-{(S)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-4-aminometil-2-bencil-benzamida,

6(S)-1-amino-N-{(5)-1-[5-cloro-4-(4-ciano-fenil)-1H-imidazol-2-il]-2-fenil-etil}-5,6,7,8-tetrahidro-isoquinolin-6-carboxamida,

6(R)-1-amino-N-{(S)-1-[5-cloro-4-(4-ciano-fenil)-1H-imidazol-2-il]-2-fenil-etil}-5,6,7,8-tetrahidro-isoquinolin-6-carboxamida,

N-{(5)-1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-4-metil-benzamida,

4-(2-{(S)-2-(3-acetilamino-fenil)-1-[(4-aminometil-ciclohexancarboxamido]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-aminometil-N-{(S)-1-[5-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-3-[(5-metil-pirazin-2-ilmetil)-carbamoil]-

propil)-ciclohexancarboxamida,

4-aminometil-N-[(S)-1-[5-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-3-(bencil-metil-carbamoil)-propil]-ciclohexancarboxamida,

4-aminometil-N-[(S)-1-[5-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-3-(bencil-carbamoil)-propil]-ciclohexancarboxamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(etil-metil-carbamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(isopropil-metil-carbamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(isobutil-metil-carbamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(metil-fenil-carbamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(etil-fenil-carbamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(metil-m-toluil-carbamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(metil-p-toluil-carbamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-[2-(1-[(4-aminometil-ciclohexancarboxamido]-2-{3-[(3-cloro-bencil)-metil-carbamoil]-fenil}-etil)-5-cloro-1H-imidazol-4-il]-benzamida,

4-[2-(1-[(4-aminometil-ciclohexancarboxamido]-2-{3-[(4-cloro-bencil)-metil-carbamoil]-fenil}-etil)-5-cloro-1H-imidazol-4-il]-benzamida,

4-[2-(1-[(4-aminometil-ciclohexancarboxamido]-2-{3-[2-(2-cloro-fenil)etilcarbarnoil]-fenil}-etil)-5-cloro-1H-imidazol-4-il]-benzamida,

4-[2-(1-[(4-aminometil-ciclohexancarboxamido]-2-{3-[2-(3-cloro-fenil)etilcarbamoil]-fenil}-etil)-5-cloro-1H-imidazol-4-il]-benzamida,

4-[2-(1-[(4-aminometil-ciclohexancarboxamido]-2-{3-[2-(4-cloro-fenil)etilcarbamoil]-fenil}-etil)-5-cloro-1H-imidazol-4-il]-benzamida,

4-aminometil-N-{(S)-1-[4-(4-metansulfonilamino-fenil)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

4-aminometil-N-[(S)-1-[5-(3-amino-1H-indazol-6-il)-1H-imidazol-2-il]-3-(ciclopropilmetil-carbamoil)-propil]-trans-ciclohexancarboxamida,

4-aminometil-N-[(S)-1-[5-(3-amino-1H-indazol-6-il)-1H-

imidazol-2-il]-3-(2-(fenil)etil-carbamoil)-propil]-trans-ciclohexancarboxamida,

4-aminometil-N-[(S)-1-[4-(4-acetilamino-fenil)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

4-aminometil-N-{(S)-1-[4-(4-hidroxi-fenil)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

4-[2-(1-[(4-aminometil-ciclohexancarboxamido]-2-{3-[metil-(2-piridin-2-il-etil)-carbamoil]-fenil}-etil)-5-cloro-1H-imidazol-4-il]-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(2,3-dihidro-indol-1-carbonil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(1,3-dihidro-isoindol-2-carbonil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(2,3-dihidro-1,4-benzoxazin-4-carbonil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-(2-{1-[(4-aminometil-ciclohexancarboxamido]-2-[3-(6-metil-3,4-dihidro-2H-quinolin-1-carbonil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-aminometil-N-{(S)-1-[4-(1H-indazol-6-il)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

1-amino-N-{(S)-1-[4-(3-amino-7-fluoro-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-trans-5,6,7,8-

tetrahidro-isoquinolin-6-carboxamida;

4-aminometil-N-{1-[4-(1H-indazol-6-il)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

4-aminometil-N-{1-[4-(3-acetilamino-fenil)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

ácido 5-(2-{1-[trans-4-aminometil-ciclohexancarboxamido]-2-fenil-etil}-5-cloro-1H-imidazol-4-il)-tiofen-2-carboxílico,

N1-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-m-imidazol-il]-2-fenil-etil}-2-cloro-tereftalamida,

4-aminometil-N-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-3-[(tiazol-2-ilmetil)-carbamoil]-propil}-trans-ciclohexancarboxamida,

4-aminometil-N-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-3-[(piridin-2-ilmetil)-carbamoil]-propil}-trans-ciclohexancarboxamida,

4-aminometil-N-{1-[5-metil-4-(3-oxo-2,3-dihidro-1H-isoindol-5-il)-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

éster de metilo del ácido[4-(2-{1-[trans-4-aminometil-ciclohexancarboxamido]-2-fenil-etil}-5-metil-1H-imidazol-4-il)-fenil]-carbámicio,

4-(2-{1-[trans-4-aminometil-ciclohexancarboxamido]-2-[3-(metil-fenil-sulfamoil)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-{2-[1-[trans-4-aminometil-ciclohexancarboxamido]-2-(3-bencensulfonil-metil-amino-fenil)-etil]-5-cloro-1H-imidazol-4-il}-benzamida,

4-(2-{1-[trans-4-aminometil-ciclohexancarboxamido]-2-[3-(benzoil-metil-amino)-fenil]-etil}-5-cloro-1H-imidazol-4-il)-benzamida,

4-aminometil-N-{1-[4-(1-imino-4-oxo-1,2,3,4-tetrahidro-ftalazin-6-il)-5-metil-1H-imidazol-2-il]-2-fenil-etil}-trans-ciclohexancarboxamida,

4-aminometil-N-(1-{5-metil-4-[3-(2H-tetrazol-5-il)-fenil]-1H-imidazol-2-il}-2-fenil-etil)-trans-ciclohexancarboxamida,

N-{1-[4-(3-amino-1H-indazol-6-il)-5-cloro-1H-imidazol-2-il]-2-fenil-etil}-2-fluoro-4-metil-benzamida,

o estereoisómeros, tautómeros, sales o solvatos farmacéuticamente aceptables de los mismos.

29. Una composición farmacéutica, caracterizada porque comprende: un portador farmacéuticamente aceptable y una cantidad terapéuticamente efectiva de un compuesto de conformidad con cualquiera de las reivindicaciones 1-28.

30. Un método para tratar un trastorno tromboembólico o inflamatorio, caracterizado porque comprende: administrar a un paciente que necesite del mismo una cantidad terapéuticamente efectiva de un compuesto de conformidad con cualquiera de las reivindicaciones 1-28.

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31. Un método para tratar un trastorno tromboembólico de conformidad con la reivindicación 30, caracterizado porque el trastorno tromboembólico se selecciona del grupo que consiste de trastorno tromboembálico cardiovascular arterial, trastorno tromboembólico cardiovascular venoso, y trastornos trornboembólicos en las cavidades del corazón.

32. Un método de conformidad con la reivindicación 31, caracterizado porque el trastorno tromboembólico se selecciona del grupo que consiste de angina inestable, un síndrome coronario agudo, fibrilación atrial, primer infarto al miocardio, infarto recurrente al miocardio, muerte isquémica repentina, ataque isquémico transitorio, apoplejía, ateroesclerosis, enfermedad arterial oclusiva periférica, trombosis venosa, trombosis de vena profunda, tromboflebitis, embolismo arterial, trombosis arterial coronaria, trombosis arterial cerebral, embolismo cerebral, embolismo de riñón, embolismo pulmonar, y trombosis que resulta de (a) válvulas prostéticas u otros implantes, (b) catéteres permanentes, (c) endoprótesis vasculares, (d) derivación cardiopulmonar, (e) hemodiálisis, y (f) otros procedimientos en los cuales la sangre se expone a una superficie artificial que promueve la trombosis.

33. Un compuesto de conformidad con cualquiera de las reivindicaciones 1-28, caracterizado porque es para su uso en la terapia.

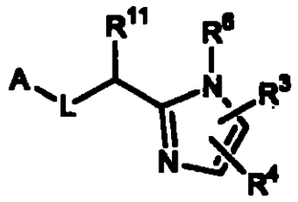
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34. El uso de un compuesto de conformidad con cualquiera de las reivindicaciones 1-28, para el fabricación de un medicamento para el tratamiento de un trastorno tromboembólico o inflamatorio.

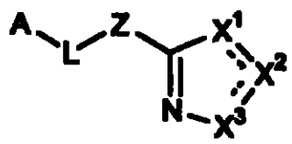
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RESUMEN DE LA INVENCION

La presente invención proporciona un método para tratar un trastorno trombótico o inflamatorio administrando a un paciente que necesita del mismo una cantidad terapéuticamente efectiva de al menos un compuesto de la fórmula (I) o Fórmula (V):



(I)



(V)

o un estereoisómero o una forma de sal o solvato farmacéuticamente aceptables del mismo, en donde las variables A, L, Z, R3, R4, R6, R11, X1, X2, y X3 son como se definen en la presente. Los compuestos de la Fórmula (I) son útiles como inhibidores selectivos de las enzimas de serina proteasa de la cascada de coagulación y/o sistema de activación por contacto; por ejemplo trombina, factor Xa, factor XIa, factor IXa, factor VIIa, y/o calicreína de plasma. En particular, se refiere a compuestos que son inhibidores selectivos del factor XIa. Esta invención también proporciona compuestos dentro del alcance de la Fórmula I y se refiere a composiciones farmacéuticas que comprenden estos compuestos.

Annex Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/US2005/021212

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It concerns the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/056784 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; PRIEPKE, HENNING; PFAU, ROL) 8 July 2004 (2004-07-08) page 1; claims	1-17, 29-34
X	WO 01/32615 A (MERCK & CO., INC; MERCK SHARP & DOHME LIMITED; THOMPSON, WAYNE; CLAREM) 10 May 2001 (2001-05-10) claims; examples	1-17, 29-34
X	WO 2004/085439 A (PFIZER PRODUCTS INC; BENBOW, JOHN, WILLIAM; CHU-MOYER, MARGARET, YUHUA) 7 October 2004 (2004-10-07) claims	1-17, 29-34
X	WO 03/035615 A (MERCK & CO., INC; TROTTER, B., WESLEY; BELL, IAN, M; ZARTMAN, C., BLAI) 1 May 2003 (2003-05-01) claims; examples	1-17, 29-34
X	WO 03/076432 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; HURNAUS, RUDOLF; RUDOLF, KL) 18 September 2003 (2003-09-18) claims	1-17, 29-34
X	WO 01/51487 A (PFIZER PRODUCTS INC; CHUPAK, LOUIS, STANLEY; DUPLANTIER, ALLEN, JACOB;) 19 July 2001 (2001-07-19) claims	1-17, 29-34

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[X] Further documents are listed in the continuation of box C.
[X] Patent family members are listed in annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

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Intern al Application No
PCT/US2005/021212

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/035510 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ; CH) 21 April 2005 (2005-04-21) page 1; claims	1-17, 29-34 780
X	WO 00/00477 A (PFIZER PRODUCTS INC; DUPLANTIER, ALLEN, JACOB; MILICI, ANTHONY, JOHN;) 6 January 2000 (2000-01-06) claims	1-17, 29-34
X	WO 02/10140 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ; TH) 7 February 2002 (2002-02-07) page 71 - page 342; claims	1-17, 29-34
X	WO 2004/071448 A (TRANSTECH PHARMA INC; MJALLI, ADNAN, M.M; ANDREWS, ROBERT, C; YARRAGUN) 26 August 2004 (2004-08-26) claims	1-17,29
X	STANFIELD, M. K. ET AL: "Synthesis of phenistidine and derivatives" JOURNAL OF ORGANIC CHEMISTRY , 30(5), 1548-50 CODEN: JOCEAH; ISSN: 0022-3263, 1965, XP009057191 the whole document	1-17,29
E	WO 2005/061496 A (ALTANA PHARMA AG; FUCHSS, THOMAS) 7 July 2005 (2005-07-07) claims; examples	1-17, 29-34
E	WO 2005/082895 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 9 September 2005 (2005-09-09) claims; examples	1-17, 29-34
E	WO 2005/056550 A (BRISTOL-MYERS SQUIBB COMPANY; LUO, GUANGLIN; CHEN, LING; DEGNAN, ANDRE) 23 June 2005 (2005-06-23) claims; examples	1-17, 29-34

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INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US2005/021212

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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17,29-34

Compounds of formula I and their use for treating thromboembolic or inflammatory disorders

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2. claims: 18-34

Compounds of formula V and their use for treating thromboembolic or inflammatory disorders

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The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows.
According to the Applicant, the problem underlying the present application is the provision of a medicament for the treatment of thromboembolic or inflammatory disorders (cf. p. 1).
The proposed solutions are compounds which are serine protease enzymes inhibitors (cf. '0013!) selected from:
a) a compound of formula I (cf. claim 1)
b) a compound of formula V (cf. claim 18)
Serine protease inhibitors such as compounds of formula I and their use as e.g. anti-thrombotic or anti-inflammatory agents are already known from e.g. D1-11.
The pharmacological property of inhibiting serine protease enzymes, respectively the treatment of thromboembolic or inflammatory disorders can no longer serve as a general inventive concept linking the two groups of compounds, which have no other special technical feature in common.
Claims 1 and 18 thus include within their scope distinct solutions which are clearly different.
In conclusion, the groups of claims are not linked by common or corresponding special technical features and define 2 different inventions not linked by a single general inventive concept. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT. Consequently, the present invention lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions listed is a distinct invention, characterized by its own technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.
Furthermore, searching this plurality of different inventions would have caused major additional searching efforts.
Only the first cited invention was searched.

The application relates to a plurality of inventions, or groups of inventions, in the sense of Rule 13.1 PCT. They have been divided as defined above. If the applicant pays additional fees for one (or more) not yet searched group(s) of invention(s), then the further search(es) may reveal further prior art that gives evidence of a further lack of

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unity 'a posteriori' within one (or more) of the not yet searched group(s). In such a case only the first invention in this (each of these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search.No further invitation to pay further additional fees will be issued. This is because Article 17(3)(a) PCT stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ('main invention') and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16).

Patent Family Annex

Information on patent family members

International Application No
PCT/US2005/021212

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Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 2004056784	A	08-07-2004	AU	2003292239	A1	14-07-2004
			CA	2510846	A1	08-07-2004
			EP	1575925	A1	21-09-2005
WO 0132615	A	10-05-2001	AU	1345401	A	14-05-2001
			CA	2389226	A1	10-05-2001
			EP	1235798	A1	04-09-2002
			JP	2003513069	T	08-04-2003
WO 2004085439	A	07-10-2004	NONE			
WO 03035615	A	01-05-2003	NONE			
WO 03076432	A	18-09-2003	AU	2003212323	A1	22-09-2003
			CA	2476031	A1	18-09-2003
			DE	10211770	A1	02-10-2003
			EP	1487821	A1	22-12-2004
			JP	2005527519	T	15-09-2005
WO 0151487	A	19-07-2001	AU	2018301	A	24-07-2001
			BG	106867	A	28-02-2003
			BR	0016818	A	01-10-2002
			CA	2396087	A1	19-07-2001
			CN	1413210	A	23-04-2003
			CZ	20022072	A3	14-05-2003
			EA	4673	B1	24-06-2004
			EE	200200372	A	15-12-2003
			EP	1244656	A1	02-10-2002
			HU	0203897	A2	28-03-2003
			JP	2003519697	T	24-06-2003
			MA	26861	A1	20-12-2004
			NO	20023085	A	26-06-2002
			NZ	518886	A	27-02-2004
			PL	357109	A1	12-07-2004
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			ZA	200205142	A	29-09-2003
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			AU	758939	B2	03-04-2003
			AU	3841699	A	17-01-2000
			BG	105190	A	31-12-2001
			BR	9911701	A	20-03-2001
			CA	2336625	A1	06-01-2000
			CN	1308616	A	15-08-2001
			CZ	20004909	A3	17-04-2002
			EA	4792	B1	26-08-2004
			EP	1091943	A1	18-04-2001
			HR	20000917	A1	28-02-2002
			HU	0102477	A2	29-05-2002
			ID	27414	A	05-04-2001
			JP	3676677	B2	27-07-2005
			JP	2002519344	T	02-07-2002
			MA	26640	A1	20-12-2004
			NO	20006600	A	21-02-2001
			NZ	508033	A	20-12-2002

Pr 1t Family Annex

Information on patent family members

Interr al Application No
PCT/US2005/021212

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0000477	A		OA	11577	A	26-07-2004
			PL	345308	A1	03-12-2001
			SK	20052000	A3	06-08-2002
			TR	200003848	T2	21-06-2001
			UA	66864	C2	17-09-2001
			ZA	9903777	A	04-12-2000
WO 0210140	A	07-02-2002	AU	7909801	A	13-02-2002
			CA	2417204	A1	07-02-2002
			CN	1444566	A	24-09-2003
			EP	1305294	A2	02-05-2003
			JP	2004518613	T	24-06-2004
			NO	20030473	A	30-01-2003
			NZ	523774	A	24-09-2004
WO 2004071448	A	26-08-2004	NONE			
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WO 2005082895	A	09-09-2005	US	2005203078	A1	15-09-2005
WO 2005056550	A	23-06-2005	US	2005153959	A1	14-07-2005

PATENT COOPERATION TRE Y

PCT/US2005/021212

10179-WO-PCT

RECEIVED

From the INTERNATIONAL BUREAU

BMS PATENT LAW

DEC 23 2005

SUN, Jing G.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

Docketed Item: 785
Due Date:
Attorney:

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing *(day/month/year)* 09 December 2005 (09.12.2005)	
Applicant's or agent's file reference 10179-PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US2005/021212	International filing date *(day/month/year)* 14 June 2005 (14.06.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 15 June 2004 (15.06.2004)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) 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.

3. *(If applicable)* 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) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) 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 or PCT receiving Office	Date of receipt of priority document
15 June 2004 (15.06.2004)	60/579,638	US	02 September 2005 (02.09.2005)
24 May 2005 (24.05.2005)	60/684,127	US	02 September 2005 (02.09.2005)
13 June 2005 (13.06.2005)	11/151,667	US	05 December 2005 (05.12.2005)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Claudio BORTON (Fax 338-8995)
Facsimile No. +41 22 338 82 70	Facsimile No. (41-22) 338.89.95 Telephone No. +41 22 338 8491

Form PCT/IB/304 (January 2004) COD9CNV9

PCT REQUEST

Original (for SUBMISSION)

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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-SAFE [EASY mode] Version 3.50 (Build 0002.162)
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	10179-PCT
I	Title of invention	FIVE-MEMBERED HETEROCYCLES USEFUL AS SERINE PROTEASE 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:	Route 206 and Province Line Road Princeton, New Jersey 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)	HANGELAND, Jon J.
III-1-5	Address:	234 Louise Drive Morrisville, Pennsylvania 19067 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

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)	QUAN, Mimi L.
III-2-5	Address:	1437 Innis Lane Yardley, Pennsylvania 19067 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)	SMALLHEER, Joanne M.
III-3-5	Address:	709 Wynnewood Drive Yardley, Pennsylvania 19067 United States of America
III-3-6	State of nationality	US
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)	BISACCHI, Gregory S.
III-4-5	Address:	72 Lincoln Street #34 Newton Highlands, Massachusetts 02461 United States of America
III-4-6	State of nationality	US
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)	CORTE, James R.
III-5-5	Address:	11 Abelia Court Lawrenceville, New Jersey 08648 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)	FRIENDS, Todd J.
III-6-5	Address:	246 Birch Hollow Drive Bordentown, New Jersey 08505 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US
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)	SUN, Zhong
III-7-5	Address:	11 Coventry Lane Hopewell, New Jersey 08525 United States of America
III-7-6	State of nationality	US
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)	ROSSI, Karen A.
III-8-5	Address:	2084 Farmview Drive Newton, Pennsylvania 18940 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)	CAVALLARO, Cullen L.
III-9-5	Address:	3 Westbury Court Robbinsville, New Jersey 08691 United States of America
III-9-6	State of nationality	US
III-9-7	State of residence	US

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)	SUN, Jing G.
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-3791
IV-1-4	Facsimile No.	609-252-4526
IV-1-6	Agent's registration No.	45,914
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	RODNEY,Burton(22,076); WANG,Joseph C.(44,391); DUNCAN,Lauralee A.(44,096); KORSEN,Elliott(32,705); GREENBLATT,Gary D.(47,609); BAXAM,Deanna L.(45,266); VANATTEN,Mary, K.(39.408); GIBBONS,Maureen(44,121); WINSLOW,Anastasia(40,875); O'BRIEN,Maureen(42,043); GOLIAN,Paul, D.(42,591); BABAJKO,Suzanne(32,880); BOGIE,Terence(44,544); BUCHHOLZ,Briana(39,123); D'AMICO,Stephen(46,652); DAVIS,Stephen(26,693); DUNCAN,Sammy(46,675); KILCOYNE,John(33,100); LAMERDIN,John(44,858); LANGE,Keith(44,201); PEIST,Kenneth(45,006); PROVOOST,Jonathan(44,292); SHER,Audrey(39,024); ALGIERI,Aldo(31,697); DUBOFF,Samuel(25,969); EPPERSON,James(52,867); MAKUJINA,Shah(41,174); RYAN,Richard(30,491); VOLLES,Warren, K.(33,810); GU,Henry(55,227); MINGO,Pamela(48,256); PARLET,Nickki L.(44,996); WILLE,Louis J.(32,954); CHIN,Jennifer T.(47,487); PATEL,Rena(41,412); KRIEGER,Stuart

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		E.(28,731); COHEN,Jacqueline M.(51,574)	
V	DESIGNATIONS		
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.		
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	15 June 2004 (15.06.2004)	
VI-1-2	Number	60/579,638	
VI-1-3	Country	US	
VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	24 May 2005 (24.05.2005)	
VI-2-2	Number	60/684,127	
VI-2-3	Country	US	
VI-3	Priority claim of earlier national application		
VI-3-1	Filing date	13 June 2005 (13.06.2005)	
VI-3-2	Number		
VI-3-3	Country	US	
VI-4	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, VI-2, VI-3	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
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	1	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1	
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	-	

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VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)). In a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from HANGELAND, Jon J. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 April 2005 (05.04.2005)
VIII-2-1(iv)		an assignment from QUAN, Mimi L. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 April 2005 (05.04.2005)
VIII-2-1(iv)		an assignment from CORTE, James R. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 April 2005 (05.04.2005)
VIII-2-1(iv)		an assignment from SMALLHEER, Joanne M. to BRISTOL-MYERS SQUIBB COMPANY, dated 06 April 2005 (06.04.2005)
VIII-2-1(iv)		an assignment from BISACCHI, Gregory S. to BRISTOL-MYERS SQUIBB COMPANY, dated 06 April 2005 (06.04.2005)
VIII-2-1(ix)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

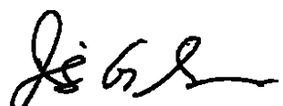
790

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VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name:	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/579,638 by virtue of the following:
VIII-3-1(iv)		an assignment from HANGELAND, Jon J. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 April 2005 (05.04.2005)
VIII-3-1(iv)		an assignment from QUAN, Mimi L. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 April 2005 (05.04.2005)
VIII-3-1(iv)		an assignment from CORTE, James R. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 April 2005 (05.04.2005)
VIII-3-1(iv)		an assignment from SMALLHEER, Joanne M. to BRISTOL-MYERS SQUIBB COMPANY, dated 06 April 2005 (06.04.2005)
VIII-3-1(iv)		an assignment from BISACCHI, Gregory S. to BRISTOL-MYERS SQUIBB COMPANY, dated 06 April 2005 (06.04.2005)
VIII-3-1(ix)	This declaration is made for the purposes of:	all designations

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	8	✓
IX-2	Description	260	-
IX-3	Claims	55	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	324	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-10	Original general power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	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)	SUN, Jing G.	
X-1-2	Name of signatory		
X-1-3	Capacity		

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	
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/EP
10-6	Transmittal 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	

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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

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			
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)		
0-9	Applicant's or agent's file reference	10179-PCT		
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee T	⇨	300	
12-2-1	Search fee S	⇨	1000	
12-2-2	International search to be carried out by	EP		
12-3	International filing fee (first 30 sheets) I1	1211		
12-4	Remaining sheets	286		
12-5	Additional amount	13		
12-6	Total additional amount I2	3718		
12-7	I1 + I2 = I	4929		
12-12	EASY Filing reduction R	-87		
12-13	Total international filing fee (I-R) I	⇨	4842	
12-14	Fee for priority document			
	Number of priority documents requested	3		
12-15	Fee per document	20		
12-16	Total priority document fee: P	⇨	60	
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇨	6202	
12-19	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.	✓		
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.	19-3880		
12-22	Date	14 June 2005 (14.06.2005)		
12-23	Name and signature	SUN, Jing G.		

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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

REMARKS

13-1-1	Applicant Remarks	The serial number for the third priority filed 13 June 2005 is unknown and will be provided. [The abstract contains chemical structures. The place where it should be inserted is indicated by brackets with the following text "INSERT CHEMICAL STRUCTURE HERE."]

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PCT

Original (for SUBMISSION)

13-1-1	Applicant Remarks	The serial number for the third priority filed 13 June 2005 is unknown and will be provided. [The abstract contains chemical structures. The place where it should be inserted is indicated by brackets with the following text "INSERT CHEMICAL STRUCTURE HERE."]

13-2-4	Validation messages Priority	Yellow Priority 3: Application No. is missing
13-2-6	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-9	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.

The present invention provides a method for treating a thrombotic or an inflammatory disorder administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I) or Formula (V

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(I) [INSERTCHEMICAL STRUCTURE HERE] (V)[INSERT CHEMICAL STRUCTURE HERE]

or a stereoisomer or pharmaceutically acceptable salt or solvate form thereof, wherein the variables A, L, Z, R3, R4, R6, R11, X1, X2, and X3 are as defined herein. The compounds of Formula (I) are useful as selective inhibitors of serine protease enzymes of the coagulation cascade and/or contact activation system; for example thrombin, factor Xa, factor XIa, factor IXa, factor VIIa and/or plasma kallikrein. In particular, it relates to compounds that are selective factor XIa inhibitors. This invention also provides compounds within the scope of Formula I and relates to pharmaceutical compositions comprising these compounds.

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PCT PETITORIO

Original (para PRESENTACION)

0 0-1	Para uso de la oficina receptora solamente Solicitud internacional No.	
0-2	Fecha internacional de registro	
0-3	Nombre de la oficina receptora y solicitud internacional ante el PCT	

0-4	Petición ante el PCT forma-PCT/RO/101	
0-4-1	Preparada usando	PCT-SAFE [modo EASY] Versión 3.50 (Build 0002.162)
0-5	Petición El abajo firmante requiere que la presente solicitud internacional sea procesada de acuerdo al Tratado Internacional en Materia de Patentes	
0-6	Oficina receptora (especificada por el solicitante)	Oficina de Patentes y Marcas de Estados Unidos (USPTO) (RO/US)
0-7	Clave de referencia del agente o solicitante	10179-PCT
I	Título de la invención	HETEROCICLOS DE CINCO MIEMBROS UTILES COMO INHIBIDORES DE LA SERINA PROTEASA
II	Solicitante	
II-1	Esta persona es:	solicitante solamente
II-2	Solicitante para	todos los Estados designados excepto US
II-4 II-5	Nombre Dirección	BRISTOL-MYERS SQUIBB COMPANY Route 206 and Province Line Road Princeton, New Jersey 08543-4000 Estados Unidos de América
II-6	Estado de nacionalidad	US
II-7	Estado de residencia	US
II-8	Teléfono No.	609-252-4000
II-9	Facsímil No.	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	solicitante e inventor
III-1-2	Solicitante para	US solamente
III-1-4 III-1-5	Nombre (ULTIMO, Primero) Dirección:	HANGELAND, Jon J. 234 Louise Drive Morrisville, Pennsylvania 19067 Estados Unidos de América
III-1-6	Estado de nacionalidad	US
III-1-7	Estado de residencia	US

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PCT PETITORIO

Original (para PRESENTACION)

III-2	Solicitante y/o inventor	
III-2-1	Esta persona es:	solicitante e inventor
III-2-2	Solicitante para:	US solamente
III-2-4	Nombre (ULTIMO, Primero)	QUAN, Mimi L.
III-2-5	Dirección:	1437 Innis Lane Yardley, Pennsylvania 19067 Estados Unidos de América
III-2-6	Estado de nacionalidad	US
III-2-7	Estado de residencia	US
III-3	Solicitante y/o inventor	
III-3-1	Esta persona es:	solicitante e inventor
III-3-2	Solicitante para:	US solamente
III-3-4	Nombre (ULTIMO, Primero)	SMALLHEER, Joanne M.
III-3-5	Dirección:	709 Wynnewood Drive Yardley, Pennsylvania 19067 Estados Unidos de América
III-3-6	Estado de nacionalidad	US
III-3-7	Estado de residencia	US
III-4	Solicitante y/o inventor	
III-4-1	Esta persona es:	solicitante e inventor
III-4-2	Solicitante para:	US solamente
III-4-4	Nombre (ULTIMO, Primero)	BISACCHI, Gregory S.
III-4-5	Dirección:	72 Lincoln Street #34 Newton Highlands, Massachusetts 02461 Estados Unidos de América
III-4-6	Estado de nacionalidad	US
III-4-7	Estado de residencia	US
III-5	Solicitante y/o inventor	
III-5-1	Esta persona es:	solicitante e inventor
III-5-2	Solicitante para:	US solamente
III-5-4	Nombre (ULTIMO, Primero)	CORTE, James R.
III-5-5	Dirección:	11 Abelia Court Lawrenceville, New Jersey 08648 Estados Unidos de América
III-5-6	Estado de nacionalidad	US
III-5-7	Estado de residencia	US

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PCT PETITORIO

Original (para PRESENTACION)

III-6	Solicitante y/o inventor	
III-6-1	Esta persona es:	solicitante e inventor
III-6-2	Solicitante para:	US solamente
III-6-4	Nombre (ULTIMO, Primero)	FRIENDS, Todd J.
III-6-5	Dirección:	246 Birch Hollow Drive Bordentown, New Jersey 08505 Estados Unidos de América
III-6-6	Estado de nacionalidad	US
III-6-7	Estado de residencia	US
III-7	Solicitante y/o inventor	
III-7-1	Esta persona es:	solicitante e inventor
III-7-2	Solicitante para:	US solamente
III-7-4	Nombre (ULTIMO, Primero)	SUN, Khong
III-7-5	Dirección:	11 Coventry Lane Hopewell, New Jersey 08525 Estados Unidos de América
III-7-6	Estado de nacionalidad	US
III-7-7	Estado de residencia	US
III-8	Solicitante y/o inventor	
III-8-1	Esta persona es:	solicitante e inventor
III-8-2	Solicitante para:	US solamente
III-8-4	Nombre (ULTIMO, Primero)	ROSSI, Karen A.
III-8-5	Dirección:	2084 Farmview Drive Newton, Pennsylvania 18940 Estados Unidos de América
III-8-6	Estado de nacionalidad	US
III-8-7	Estado de residencia	US
III-9	Solicitante y/o inventor	
III-9-1	Esta persona es:	solicitante e inventor
III-9-2	Solicitante para:	US solamente
III-9-4	Nombre (ULTIMO, Primero)	CAVALLARO, Cullen L.
III-9-5	Dirección:	3 Westbury Court Robbinsville, New Jersey 08691 Estados Unidos de América
III-9-6	Estado de nacionalidad	US
III-9-7	Estado de residencia	US

PCT PETITORIO

Original (para PRESENTACION)

IV-1	Agente o representante común o dirección para correspondencia La persona identificada posteriormente es por lo tanto/ha sido designada para actuar en beneficio del solicitante(s) ante las Autoridades Internacionales competentes como:	agente
IV-1-1	Nombre (Ultimo, Primero)	SUN, Jing G.
IV-1-2	Dirección:.	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No:	609-252-3791
IV-1-4	Facsimil No.:	609-252-4526
IV-1-5	Registro del Agente No.	45,914
IV-2	Agente(s) adicional(es)	Agentes adicionales con la misma dirección como el primer agente nombrado
IV-2-1	Nombre(ULTIMO, primero)	RODNEY, Burton (22,076); KANG, Joseph C. (44,391); DUNCAN, Laureles A. (44,096); KORSEN, Elliott (32,705); GREENBLATT, Gary D. (47,609); BAXAM, Deanna L. (45,266); VANATTEN, Mary, K. (39,408); WINSLOW, Anastasia (40,875); O'BRIEN, Maureen (42,043); GOLIAN, Paul, D. (42,591); BABAJKO, Suzanne (32,880); BOGIE, Terence (44,544); BUCHHOLZ, Briana (39,123); D'AMICO, Stephen (46,652); DAVIS, Stephen (26,693); DUNCAN, Sammy (46,675); KILCOYNE, John (33,100); LAMERDIN, John (44,858); LANGE, Keith (44,201); PEIST, Kenneth (45,006); PROVOOST, Jonathan (44,292); SHER, Audrey (39,024); ALGIERI, Aldo (31,697); DUBOFF, Samuel (25,969); EPPERSON, James (52,867); MAKUJINA, Shah (41,174); RYAN, Richard (30,491); VOLLES, Warren, K. (33,810); GU, Henry (55,227); MINGO, Pamela (48,256); PARLET, Nickki L. (44,996); WILLE, Louis J. (32,954); CHIN, Jennifer T. (47,487); PATEL, Rena (41,412); KRIEGER, Stuart E. (28,731); COHEN, Jacqueline M. (51,574)
IV-2-2	Dirección	

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PCT PETITORI

Original (para PRESENTACION)

V	DESIGNACIONES		
V-1	La presentación de esta solicitud constituye bajo la Regla 4.9(a), la designación de todos los Estados Contratantes unidos por el PCT en la fecha de presentación internacional, para otorgar cada clase de protección disponible y, donde sea aplicable, para otorgar tanto patentes regional como nacional.		
VI-1	Reivindicación prioritaria de la primera solicitud nacional		
VI-1-1	Fecha de presentación	15 Junio 2004 (15.06.2004)	
VI-1-2	Número	60/579,638	
VI-1-3	País	US	
VI-2	Reivindicación prioritaria de la primera solicitud nacional		
VI-2-1	Fecha de presentación	24 Mayo 2005 (24.05.2005)	
VI-2-2	Número	60/684,127	
VI-2-3	País	US	
VI-3	Reivindicación prioritaria de la primera solicitud nacional		
VI-3-1	Fecha de presentación	13 Junio 2005 (13.06.2005)	
VI-3-2	Número		
VI-3-3	País	US	
VI-4	Solicitud del documento de prioridad Se solicita a la oficina receptora preparar y transmitir a la Oficina Internacional una copia certificada de la solicitud más anticipada identificada anteriormente como punto(s):	VI-1, VI-2, VI-3	
VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina Europea de Patentes(EPO) (ISA/EP)	
VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración relativa a la identidad del inventor	-	
VIII-2	Declaración relativa al derecho del solicitante, a la fecha de presentación internacional de solicitar y de obtener una patente	1	
VIII-3	Declaración relativa al derecho del solicitante, a la fecha de presentación internacional de reivindicar la prioridad de la solicitud anterior	1	
VIII-4	Declaración relativa a la cualidad de inventor (solamente con fines de la designación de los Estados Unidos de América	-	
VIII-5	Declaración relativa a las divulgaciones no oponibles o a las excepciones por falta de novedad	-	

PCT PETITORIO

Original (para PRESENTACION)

VIII-2-1	Declaración: Autorización para solicitar y otorgar una patente Declaración en cuanto a la autorización del solicitante, en cuanto a la fecha de presentación internacional, para solicitar y otorgar una patente (Reglas 4.17(ii) y 51bis.1(a)(ii)), en un caso en donde la declaración bajo la Regla 4.17(iv) no sea apropiada: -Nombre:	en relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY se autoriza para solicitar y para que se le otorgue una patente en virtud de lo siguiente:
VIII-2-1 (iv)		una cesión de HANGELAND, Jon J. para BRISTOL-MYERS SQUIBB COMPANY, fechada 05 Abril 2005 (05.04.2005)
VIII-2-1 (iv)		una cesión de QUAN, Mimi L. para BRISTOL-MYERS SQUIBB COMPANY, fechada 05 Abril 2005 (05.04.2005)
VIII-2-1 (iv)		una cesión de CORTE, James R. para BRISTOL-MYERS SQUIBB COMPANY, fechada 05 Abril 2005 (05.04.2005)
VIII-2-1 (iv)		una cesión de SMALLHEER, Joanne M. para BRISTOL-MYERS SQUIBB COMPANY, fechada 06 Abril 2005 (06.04.2005)
VIII-2-1 (iv)		una cesión de BISACCHI, Gregory S. para BRISTOL-MYERS SQUIBB COMPANY, fechada 06 Abril 2005 (06.04.2005)
VIII-2-1 (ix)	Se realiza esta declaración para los propósitos de:	todas las designaciones excepto la designación de los Estados Unidos de América

PCT PETITORIO

Original (para PRESENTACION)

VIII-3-1	Declaración: Autorización para reivindicar la prioridad Declaración en cuanto a la autorización del solicitante, en cuanto a la fecha de presentación internacional, para reivindicar la prioridad de la solicitud más temprana especificada posteriormente, donde el solicitante no es el solicitante quien presenta la solicitud más temprana o donde el nombre del solicitante ha cambiado desde la presentación de la solicitud más temprana (Reglas 4.17(iii) y 51bis.1(a)(iii)): Nombre:	en relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY se autoriza para reivindicar la prioridad de la solicitud más anticipada No. 60/579,638 en virtud de lo siguiente:
VIII-3-1 (iv)		una cesión de HANGELAND, Jon J. para BRISTOL-MYERS SQUIBB COMPANY, fechada 05 Abril 2005 (05.04.2005)
VIII-3-1 (iv)		una cesión de QUAN, Mimi L. para BRISTOL-MYERS SQUIBB COMPANY, fechada 05 Abril 2005 (05.04.2005)
VIII-3-1 (iv)		una cesión de CORTE, James R. para BRISTOL-MYERS SQUIBB COMPANY, fechada 05 Abril 2005 (05.04.2005)
VIII-3-1 (iv)		una cesión de SMALLHEER, Joanne M. para BRISTOL-MYERS SQUIBB COMPANY, fechada 06 Abril 2005 (06.04.2005)
VIII-3-1 (iv)		una cesión de BISACCHI, Gregory S. para BRISTOL-MYERS SQUIBB COMPANY, fechada 06 Abril 2005 (06.04.2005)
VIII-3-1 (ix)	Se hace esta declaración para los propósitos de:	todas las designaciones

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PCT PETITORI

Original (para PRESENTACION)

IX	Lista de verificación	Número de hojas	Archivos electrónicos relacionados
IX-1	Petitorio (incluyendo las hojas para declaración)	8	√
IX-2	Descripción	260	–
IX-3	Reivindicaciones	55	–
IX-4	Resumen	1	√
IX-5	Dibujos	0	–
IX-7	TOTAL	324	
	Artículos anexos	Papel o documento(s) unidos	Campos electrónicos unidos
IX-8	Hoja de cálculo de honorarios	√	–
IX-10	Poder general original del apoderado	√	–
IX-17	Medio físico PCT-SAFE	–	√
IX-19	No de Figura de los dibujos que debería acompañar al resumen		
IX-20	Idioma de registro de la solicitud internacional	Inglés	
X-1	Firma del solicitante, agente o representante común	(rúbrica)	
X-1-1	Nombre (Apellido, Nombre)	SUN, Jing G.	
X-1-2	Nombre del firmante		
X-1-3	Capacidad		

PARA USO DE LA OFICINA RECEPTORA UNICAMENTE

10-1	Fecha de la recepción del contenido de la solicitud internacional	
10-2 10-2-1 10-2-2	Dibujos Recibidos No recibidos	
10-3	Fecha corregida de la recepción actual debido a recepción última pero a tiempo de papeles o dibujos que completan el contenido de la solicitud internacional	
10-4	Fecha de la recepción a tiempo de las correcciones requeridas bajo el Artículo 11(2) del PCT	
10-5	Autoridad de Búsqueda Internacional	ISA/EP
10-6	Transmisión de la copia de búsqueda retrasada hasta que los honorarios estén pagados	

PARA USO DE LA OFICINA INTERNACIONAL SOLAMENTE

11-1	Fecha de la recepción de la copia del documento por la Oficina Internacional	

Anexo de la Forma PCT/ISA/206
COMUNICACION CON RELACION A LOS RESULTADOS DE LA BUSQUEDA INTERNACIONAL PARCIAL

No. de Solicitud Internacional
PCT/US2005/021212 806

1. La presente comunicación es un Anexo a la invitación para pagar honorarios adicionales (Forma PCT/ISA/206). Muestra los resultados de la búsqueda internacional establecida en las partes de la solicitud internacional los cuales se refieren a la invención mencionada primero en las reivindicaciones Nos.:
VER 'INVITACION PARA PAGAR HONORARIOS ADICIONALES'
2. Esta comunicación no es el reporte de búsqueda internacional el cual se establecerá de acuerdo con el Artículo 18 y Regla 43.

3. Si el solicitante no paga cualquier honorario de búsqueda adicional, la información que aparece en esta comunicación será considerada como el resultado de la búsqueda internacional y será incluida en el reporte de búsqueda internacional.

4. Si el solicitante paga honorarios adicionales, el reporte de búsqueda contendrá la información que aparece en esta comunicación y los resultados de la búsqueda internacional en otras partes de la solicitud internacional para la cual tales honorarios se habían pagado.

C. DOCUMENTOS QUE SE CONSIDERAN PERTINENTES

Categoría*	Citación del documento, con indicación, donde es apropiado, de los pasajes pertinentes	Pertinente para la reivindicación No.
X	WO 2004/056784 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; PRIEPKE, HENNING; PFAU. ROL) 8 Julio 2004 (2004-07-08) página 1; reivindicaciones	1-17, 29-34
X	WO 01/32615 A (MERCK & CO., INC; MERCK SHARP & DOHME LIMITED; THOMPSON, WAYNE; CLAREM) 10 MAYO 2001 (2001-05-10) reivindicaciones; ejemplos	1-17, 29-34
X	WO 2004/085439 A (PFIZER PRODUCTS INC; BENBOW, JOHN, WILLIAM; CHU-MOYER, MARGARET, YUHUA) 7 Octubre 2004 (2004-10-07) reivindicaciones	1-17, 29-34
X	WO 03/035615 A (MERCK & CO., INC; TROTTER, B., WESLEY; BELL, IAN, M; ZARTMAN, C., BLAI) 1 Mayo 2003 (2003-05-01) reivindicaciones; ejemplos	1-17, 29-34
X	WO 03/078432 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; HURNAUS, RUDOLF; RUDOLF, KL) 18 Septiembre 2003 (2003-09-18) reivindicaciones	1-17, 29-34
X	WO 01/51487 A (PFIZER PRODUCTS INC; CHUPAK, LOUIS, STANLEY; DUPLANTIER, ALLEN, JACOB:) 19 Julio 2001 (2001-07-19) reivindicaciones	1-17, 29-34
	--/--	

☒ Documentos adicionales se listan en la continuación del cuadro C. ☒ Los miembros de la familia de patentes se listan en el anexo

* Categoría especial de los documentos citados:

"A" Documento que define el estado general de la técnica, que no se considera que es de pertinencia particular
"E" Documento anterior, pero publicado en o después de la fecha de presentación internacional
"L" Documento que puede crear dudas de la reivindicación(es) de prioridad o que se cita para establecer la fecha de publicación de otra situación u otra razón especial (como se especifique)
"O" Documento que se refiere a una descripción oral, uso, exhibición u otro medio
"P" Documento publicado antes de la fecha de presentación internacional, pero después de la fecha de prioridad reivindicada
"T" Documento posterior publicado después de la fecha de presentación internacional o la fecha de prioridad, y que no provoca conflicto con la solicitud, pero se cita para entender el principio o teoría que trata la invención
"X" Documento de pertinencia particular; la invención reivindicada no se puede considerar nueva o no se puede considerar que comprende un paso inventivo cuando el documento se toma solo
"Y" Documento de pertinencia particular; la invención reivindicada no se puede considerar que comprende un paso inventivo cuando el documento se combina con uno o más de estos documentos, estas combinaciones son obvias para una persona experta en la técnica
"&" Documento miembro de la familia de patentes

REPORTE DE BÚSQUEDA INTERNACIONAL

No. Solicitud Internacional
PCT/US2005/021212

DOCUMENTOS QUE SE CONSIDERAN PERTINENTES (continuación)

Categoría*	Citación del documento, con indicación, donde es apropiado, de los pasajes pertinentes	Pertinente para la Reivindicación No.
X	WO 2005/035510 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ; CH) 21 Abril 2005 (2005-04-21) página 1; reivindicaciones	1-17, 29-34 807
X	WO 00/00477 A (PFIZER PRODUCTS INC ; DUPLANTIER, ALLEN, JACOB ; MILICI, ANTHONY, JOHN ;) 6 Enero 2000 (2000-01-06) reivindiaciones	1-17, 29-34
X	WO 02/10140 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES; TH) 7 Febrero 2002 (2002-02-07) página 71 – página 342; reivindicaciones	1-17, 29-34
X	WO 2004/071448 A (TRANSTECH PHARMA INC; MJALLI, ADNAN, M.M ; ANDREWS, ROBERT, C; YARRAGUN) 26 Agosto 2004 (2004-08-26) reivindicaciones	1-17, 29
X	STANFIELD, M. K. ET AL : "Synthesis of phenistidine and derivatives" JOURNAL OF ORGANIC CHEMISTRY, 30(5), 1548-50 CODEN : JOCEAH ; ISSN : 0022-3263, 1965, XP009057191 el documento completo	1-17, 29
E	WO 2005/061496 A (ALTANA PHARMA AG; FUCHSS, THOMAS) 7 Julio 2005 (2005-07-07) reivindicaciones; ejemplos	1-17, 29-34
E	WO 2005/082895 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 9 Septiembre 2005 (2005-09-09) reivindicaciones; ejemplos	1-17, 29-34
E	WO 2005/056550 A (BRISTOL-MYERS SQUIBB COMPANY ; LUO, GUANGLIN; CHEN, LING; DEGNAN, ANDRE) 23 Junio 2005 (2005-06-23) reivindicaciones; ejemplos	1-17, 29-34

INVITACION PARA PAGAR HONORARIOS ADICIONALES

No. de Solicitud Internacional
PCT/US2005/021212

Esta Autoridad de Búsqueda Internacional encontró múltiples (grupos de) invenciones en esta solicitud internacional, como sigue:

1. reivindicaciones: 1-17, 29-34

Compuestos de fórmula I y su uso para tratar trastornos tromboembólicos

---

2. reivindicaciones: 18-34

Compuestos de la fórmula V y su uso para tratar trastornos tromboembólicos o inflamatorios

---

Las razones por la cual las invenciones no se enlazan para formar un concepto inventivo general único, como se requiere por la Regla 13.1 del PCT, son como sigue.

De acuerdo con el solicitante, el problema fundamental de la presente solicitud es la provisión de un medicamento para el tratamiento de trastornos tromboembólicos o inflamatorios (cotéjese, p. 1).

Las soluciones propuestas son compuestos los cuales son inhibidores de las enzimas serina proteasa (cotéjese '0013!) seleccionados de:

a) un compuesto de la fórmula I (cotéjese reivindicación 1)

b) un compuesto de la fórmula V (cotéjese reivindicación 18)

Los inhibidores de serina proteasa tales como los compuestos de la fórmula I y su uso como agentes anti-trombóticos o anti-inflamatorios son ya conocidos de por ejemplo D1-11.

La propiedad farmacológica de la inhibición de enzimas serina proteasa, respectivamente el tratamiento de trastornos tromboembólicos o inflamatorios no puede servir más tiempo como un concepto inventivo general que enlaza los dos grupos de compuestos, los cuales no tienen otra característica técnica especial en común. Las reivindicaciones 1 y 18 por consiguiente incluyen dentro de su alcance distintas soluciones las cuales son claramente diferentes.

En conclusión, los grupos de reivindicaciones no se enlazan por

características técnicas especiales correspondientes o comunes y definen 2 diferentes invenciones no enlazadas por un concepto inventivo general único. La solicitud, por lo tanto no cumple los requerimientos de unidad de invención como se define en las reglas 13.1 y 13.2 del PCT. En consecuencia, la presente invención carece de unidad de invención, y las diferentes soluciones que no pertenecen a un concepto inventivo común se identifican como los diferentes objetos listados anteriormente. Cada una de las invenciones listadas es una invención distinta, caracterizada por su propia característica técnica, definiendo la contribución la cual cada una de las invenciones reivindicadas, considerada como un todo, hace sobre la técnica previa.
Además, buscar esta pluralidad de diferentes invenciones podría haber originado mayores esfuerzos de búsqueda adicionales.
Solamente la primera invención citada se buscó.

La solicitud se refiere a una pluralidad de invenciones, o grupos de invenciones, en el sentido de la Regla 13.1 del PCT. Se han dividido como se definió anteriormente. Si el solicitante paga honorarios adicionales para uno (o más) grupo(s) todavía no buscado(s) de las invenciones, entonces las búsquedas adicionales pueden revelar adicionalmente técnica previa que da evidencia de una carencia de unidad adicional dentro de uno (o más) de los grupos todavía no buscados. En tal caso solamente la primera invención en estos (cada uno de estos) grupo(s) de invenciones, que se considera que carece de unidad de invención, será sometida a una búsqueda. Ninguna invitación adicional a pagar nuevos honorarios adicionales será emitida. Esto es debido a que el Artículo 17(3)(a) del PCT estipula que la ISA deberá establecer el Reporte de Búsqueda Internacional en aquellas partes de la solicitud internacional la cual se refiere a la invención mencionada primero en las reivindicaciones ('invención principal') y para aquellas partes las cuales se refieren a invenciones con respecto a las cuales los honorarios adicionales se pagaran. Ni el PCT ni las directrices del PCT proporcionar una base legal para invitaciones adicionales a pagar nuevos honorarios de búsqueda adicionales (W17/00, punto 11 y W1/97, puntos 11-16).

REPORTE DE BUSQUEDA INTERNACIONAL

Información sobre los miembros de familia de patentes

Solicitud Internacional No.: PCT/US2005/021212

Documento de la patente citado en el reporte de búsqueda		Fecha de Publicación	Miembros de la familia de patentes		Fecha de Publicación
WO 2004056784	A	08-07-2004	AU	2003292239 A1	14-07-2004
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WO 03076432	A	18-09-2003	AU	2003212323 A1	22-09-2003
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			JP	2002519344 T	02-07-2002
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			NZ	508033 A	20-12-2002

REPORTE DE BUSQUEDA INTERNACIONAL

Información sobre los miembros de familia de patentes

Solicitud Internacional No.: PCT/US2005/021212

Documento de la patente citado en el reporte de búsqueda	Fecha de Publicación	Miembros de la familia de patentes		Fecha de Publicación
WO 0000477 A		OA	11577 A	26-07-2004
		PL	345308 A1	03-12-2001
		SK	20052000 A3	06-08-2002
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WO 2005056550 A	23-06-2005	US	2005153959 A1	14-07-2005

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

812

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL

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

4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

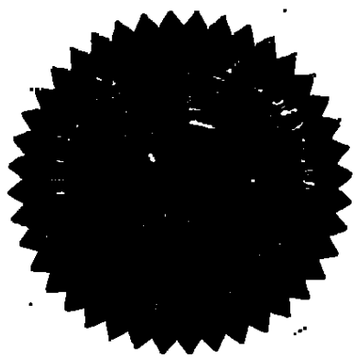
6. THE 13TH DAY OF JANUARY 2006

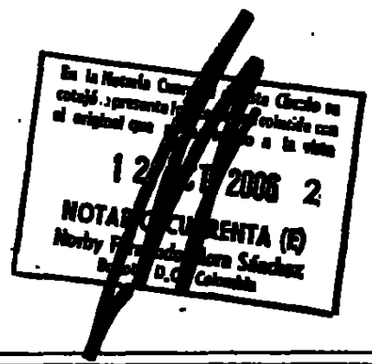
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A248886

9. SEAL/STAMP:

10. SIGNATURE





Brigard & Castro

BOGOTA - COLOMBIA

871

813

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales ecesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciled in Princeton, New Jersey, USA

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO**, and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

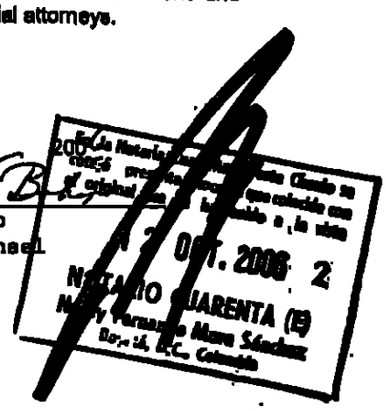
Granted and signed in

this 11th day Jan of 200

Signature

Suzanne E. Babajko

Name Senior Patent Counsel
Title



814

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del objeto social de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 11 day of January of 2006 personally appeared before me SUZANNE E. BABAJKO

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
SENIOR PATENT COUNSEL

of BRISTOL-MYERS SQUIBB COMPANY

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of
under date of

and that he (she) who grants the present power of attorney is its Representative.

Public Notary (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

[illegible] de de , compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this 11th day of January of 2006
personally appeared before me
Suzanne E. Babajko
who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Maura O. Knobl
Notary Public
MAURA O. KNOBL
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires July 9, 2008

En la Notaría Cuarenta y Dos del Círculo se extendió el presente fotocopiado que concuerda con el original que se tuvo a la vista
12 OCT 2006
NOTARIO CUARENTA Y DOS (E)

LEGALIZACION POR APOSTILLA ES REQUERIDA

LEGALIZATION BY APOSTILLE IS REQUIRED.

815

TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en **Princeton, New Jersey, Estados Unidos de América.**

APOSTILLA

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

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PUBLICO HA SIDO FIRMADO POR:
MAURA O KNOBL

3. ACTUANDO EN CAPACIDAD DE:
NOTARIO PUBLICO DE NEW JERSEY

4. LLEVA EL SELLO/TIMBRE DE:
MAURA O KNOBL, NOTARIO

CERTIFICADO

5. EN TRENTON, NEW JERSEY

6. EL 13 DE ENERO DE 2006

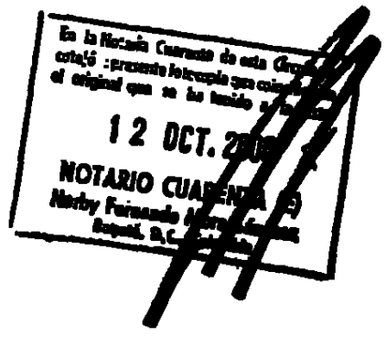
7. POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY

8. NO. A248886

9. SELLO/TIMBRE:

10. FIRMA

(Firma)



844

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radi: 08-125883- -00000-0000
Fec: 2008-12-15 16:54:39 Usp: SIC NUEVOS AUXILIARES
Tra: 11 PATENTES
Eve: 378 PRESENTACION
Act 411 PRESENTACION Folios: 013

816

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

817

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
BRISTOL MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	06 125963
	Solicitud internacional	PCT/US2005/021212
	Fecha inicio fase nacional	15/01/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	[illegible]858

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:

1. 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 Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 26 ENE. 2007
adpa10