SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 05-58718

54 **TITULO** COMPUESTOS DE PIRAZOL ACICLICO PARA LA INHIBICION DE PROTEINA CINASA-2 ACTIVADA POR PROTEINA CINASA ACTIVADA POR MITOGENOS

51 **CLASIFICACION INTERNACIONAL** C 07 D 401/04
C 07 D 471/04

71 **SOLICITANTE** PHARMACIA CORPORATION

DOMICILIO CHESTERFIELD, MISSOURI 63017-1732, ESTADOS UNIDOS

74 **APODERADO** HECTOR GOMEZ MEJIA

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

PETITORIO

AS: 97.382

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **PHARMACIA CORPORATION** Dirección: 700 Chesterfield Parkway West Chesterfield, Missouri 63017-1732, 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: HECTOR GOMEZ MEJIA Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 22720 TP 19436
4 INVENTOR (ES) (72)	Nombre: Cathleen E. Hanau, Serena Marie Mershon, Matthew J. Granato, Marvin J. Meyers, Shridhar G. Hegde, Ingrid P. Buchler, Kun K. Wu, Shuang Liu, Kassoom Nacro Dirección: 15551 Wendimill Drive, Chesterfield, MO 63017, US; 303 Spring Street, Bessemer, MI 49911 , US; 352 Hartwell Ct., Chesterfield, MO 63017, US; 4006 Summerfield Parkway, Saint Charles, MO 63304, US; 130 Holly Garden Drive, Ballwin, MO 63021, US; 7627 Delmar Blvd., Apt. 2, South University City, MO 63130, US; 1101-I Olive Lake Drive, St. Louis, MO 63132, US; 302 Polsinelli Dr., Schenectady, NY 12303, US; 106 Teneyck Place, Apt. 10, Guilderland, NY 12084, Estados Unidos de América (Respectivamente) Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

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6 Título (54): COMPUESTOS DE PIRAZOL ACÍCLICO PARA LA INHIBICIÓN DE PROTEÍNA CINASA-2 ACTIVADA POR PROTEÍNA CINASA ACTIVADA POR MITÓGENOS

7 Clasificación Internacional (51) _____

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

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $443.000
- [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 Tarjeta de Propietarios

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente

NOMBRE: HECTOR GOMEZ MEJIA

FIRMA:

C.C. 2720 de Bogotá T.P. 10[illegible] del C.S.J.

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

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BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	28252183	02/06/2005	21.261,000.00

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

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1	50003-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

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(71) Applicant (*for all designated States except US*): PHARMACIA CORPORATION [US/US]; Mail Zone MC5S, 575 Maryville Centre Drive, St. Louis, MO 63141 (US).

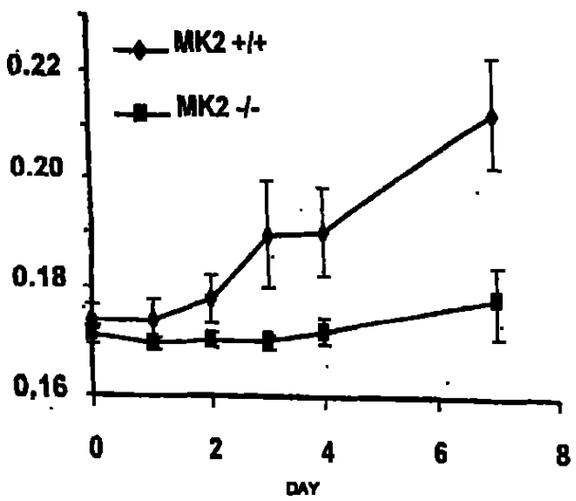
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): HANAU, Cathleen, E. [US/US]; 15551 Wendimill Drive, Chesterfield, MO 63017 (US). MERSHON, Serena, Marie [US/US]; 303 Spring Street, Bessemer, MI 49911 (US). GRANETO, Matthew, J. [US/US]; 352 Hartwell Ct., Chesterfield, MO 63017 (US). MEYERS, Marvin, J. [US/US]; 4006 Summerfield Parkway, Saint Charles, MO 63304 (US). HEGDE, Shridhar, G. [US/US]; 130 Holly Garden Drive, Ballwin, MO 63021 (US). BUCHLER, Ingrid, P. [US/US]; 7627 Delmar Blvd., Apt. 2, South University City, MO 63130 (US). WU, Kun, K. [CA/US]; 1101-I Olive Lake Drive, St. Louis, MO 63132 (US). LIU, Shaung [CN/US]; 302 Polsinelli Dr., Schenectady, NY 12303 (US). NACHO, Kassoum [BF/US]; 106 Teneyck Place, Apt. 10, Guilderland, NY 12084 (US).

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[Continued on next page]

(54) Title: ACYCLIC PYRAZOLE COMPOUNDS FOR THE INHIBITION OF MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2



(57) Abstract: Compounds are described which inhibit mitogen activated protein kinase-activated protein kinase-2 (MK-2). Methods of making such compounds are described, as well as a method of using them for the inhibition of MK-2, and for the prevention or treatment of a disease or disorder that is mediated by TNFα, where the method involves administering to the subject an MK-2 inhibiting compound of the present invention. Pharmaceutical compositions and kits which contain the present MK-2 inhibiting compounds are also described.

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ACYCLIC PYRAZOLE COMPOUNDS FOR THE INHIBITION OF MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2

CROSS REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

[0001] This application is related to and claims the benefit of U.S. Provisional Patent Application Serial No. 60/434,962, filed December 20, 2002, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates to certain cyclic and heterocyclic compounds which inhibit mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2, or MK-2), and also to methods of using such compounds to inhibit MK-2 and for the prevention and treatment of TNFα mediated diseases or disorders in subjects that are in need of such prevention and/or treatment.

(2) Description of the Related Art:

[0003] Mitogen-activated protein kinases (MAPKs) are members of conserved signal transduction pathways that activate transcription factors, translation factors and other target molecules in response to a variety of extracellular signals. MAPKs are activated by phosphorylation at a dual phosphorylation motif with the sequence Thr-X-Tyr by mitogen-activated protein kinase kinases (MAPKKs). In higher eukaryotes, the physiological role of MAPK signaling has been correlated with cellular events such as proliferation, oncogenesis, development and differentiation. Accordingly, the ability to regulate signal transduction via these pathways could lead to the development of treatments and preventive therapies for human diseases associated with MAPK signaling, such as inflammatory diseases, autoimmune diseases and cancer.

[0004] In mammalian cells, three parallel MAPK pathways have been described. The best characterized pathway leads to the activation of the extracellular-signal-regulated kinase (ERK). Less well understood are the

signal transduction pathways leading to the activation of the cJun N-terminal kinase (JNK) and the p38 MAPK. See, *e.g.*, Davis, *Trends Biochem. Sci. 19*:470-473 (1994); Cano, *et al., Trends Biochem. Sci. 20*:117-122(1995).

[0005] The p38 MAPK pathway is potentially activated by a wide variety of stresses and cellular insults. These stresses and cellular insults include heat shock, UV irradiation, inflammatory cytokines (such as TNF and IL-1), tunicamycin, chemotherapeutic drugs (*i.e.*, cisplatinum), anisomycin, sorbitol/hyperosmolarity, gamma irradiation, sodium arsenite, and ischaemia. See, Ono, K., *et al, Cellular Signalling 12*, 1 - 13 (2000). Activation of the p38 pathway is involved in (1) production of proinflammatory cytokines, such as TNF-α; (2) induction of enzymes, such as Cox-2; (3) expression of an intracellular enzyme, such as INOS, which plays an important role in the regulation of oxidation; (4) induction of adherent proteins, such as VCAM-1 and many other inflammatory-related molecules. Furthermore, the p38 pathway functions as a regulator in the proliferation and differentiation of cells of the immune system. See, Ono, K., *et al., Id.* at 7.

[0006] The p38 kinase is an upstream kinase of mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2 or MK-2). (See, Freshney, N. W., *et al., J. Cell, 78*:1039-1049 (1994)). MK-2 is a protein that appears to be predominantly regulated by p38 in cells. Indeed, MK-2 was the first substrate of p38α to be identified. For example, *in vitro* phosphorylation of MK-2 by p38α activates MK-2. The substrates that MK-2 acts upon, in turn, include heat shock protein 27, lymphocyte-specific protein 1 (LAP1), cAMP response element-binding protein (CREB), ATF1, serum response factor (SRF), and tyrosine hydroxylase. The substrate of MK-2 that has been best characterized is small heat shock protein 27 (hsp27).

[0007] The role of the p38 pathway in inflammatory-related diseases has been studied in several animal models. The pyridinyl imidazole compound SB203580 has been shown to be a specific inhibitor of p38 *in*

vivo, and also has been shown to inhibit activation of MK-2, (See, Rouse, J., *et al, Cell, 78*:1027-1037 (1994); Cuenda, A., *et al, Biochem. J.*, 333:11-15 (1998)), as well as a MAP kinase homologue termed reactivating kinase (RK). (See, Cuenda, A., *et al., FEBS Lett., 364(2)*:229 - 233 (1995)). Inhibition of p38 by SB203580 can reduce mortality in a murine model of endotoxin-induced shock and inhibit the development of mouse collagen-induced arthritis and rat adjuvant arthritis. See, *e.g.*, Badger, A. M., *et al., J. Pharmacol Exp. Ther., 279*:1453 - 1461 (1996). Another p38 inhibitor that has been utilized in an animal model that is believed to be more potent than SB203580 in its inhibitory effect on p38 is SB 220025. A recent animal study has demonstrated that SB 220025 caused a significant dose-dependent decrease in vascular density of granulomas in laboratory rats. (See, Jackson, J. R., *et al, J. Pharmacol. Exp. Ther., 284*:687 - 692 (1998)). The results of these animal studies indicated that p38, or the components of the p38 pathway, can be useful therapeutic targets for the prevention or treatment of inflammatory disease.

[0008] Due to its integral role in the p38 signaling pathway, MK-2 has been used as a monitor for measuring the level of activation in the pathway. Because of its downstream location in the pathway, relative to p38, MK-2 has been measured as a more convenient, albeit indirect, method of assessing p38 activation. However, so far, research efforts exploring therapeutic strategies associated with the modulation of this pathway have focused mainly on the inhibition of p38 kinase.

[0009] Several compounds that inhibit the activity of p38 kinase have been described in U.S. Patent Nos. 6,046,208, 6,251,914, and 6,335,340. These compounds have been suggested to be useful for the treatment of CSBP/RK/p38 kinase mediated disease. Commercial efforts to apply p38 inhibitors have centered around two p38 inhibitors, the pyridinylimidazole inhibitor SKF 86002, and the 2,4,5 triaryl imidazole inhibitor SB203580. See, Lee, J. C., *et al, Immunopharmacology 47*, 185-192 (2000). Compounds possessing a similar structure have also been investigated as

potential p38 inhibitors. Indeed, p38 MSP kinase's role in various disease states has been elucidated through the use of inhibitors.

[00010] Kotlyarov, A. *et al*, in *Nat. Cell Biol., 1(2)*:94 - 97 (1999) introduced a targeted mutation into a mouse MK-2 gene, resulting in MK-2-deficient mice. It was shown that mice lacking MK-2 possessed increased stress resistance and survived LPS-induced endotoxic shock better than MK-2$^+$ mice. The authors concluded that MK-2 was an essential component in the inflammatory response that regulates biosynthesis of TNFα at a post-transcriptional level. More recently, Lehner, M.D., *et al*, in *J. Immunol., 168(9)*:4667-4673 (2002), reported that MK-2-deficient mice showed increased susceptibility to *Listeria monocytogenes* infection, and concluded that MK-2 had an essential role in host defense against intracellular bacteria, probably via regulation of TNF and IFN-gamma production required for activation of antibacterial effector mechanisms.

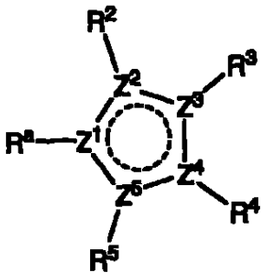
[00011] The location of MK-2 in the p38 signaling pathway at a point that is downstream of p38 offers the potential that MK-2 could act as a focal point for modulating the pathway without affecting as many substrates as would the regulation of an enzyme further upstream in the signaling cascade – such as p38 MAP kinase.

[00012] Accordingly, it would be useful to provide compounds and methods that could serve to modulate the activity of MK-2 – in particular, to act as inhibitors of MK-2 activity. Such compounds and methods would be useful for the provision of benefits similar to p38 MAP kinase inhibitors, which benefits include the prevention and treatment of diseases and disorders that are mediated by TNFα. It would be even more useful to provide MK-2 inhibitors having improved potency and reduced undesirable side effects, relative to p38 inhibitors.

SUMMARY OF THE INVENTION

[00013] Briefly therefore, the present invention is directed to a novel compound having the structure of formula I:

Formula I:

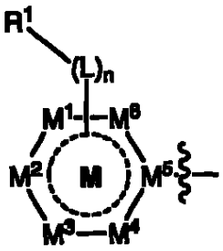


wherein:

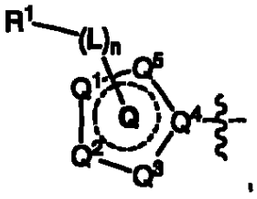
Z^2 and Z^3 are nitrogen, Z^1, Z^4 and Z^5 are carbon, and join with Z^2 and Z^3 to form a pyrazole ring, or optionally, Z^4 and Z^5 are nitrogen, Z^1, Z^2 and Z^3 are carbon and join with Z^4 and Z^5 to form a pyrazole ring;

R^a is selected from:

1)

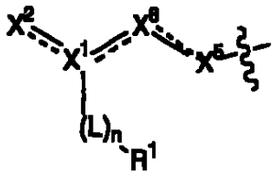


2)



, and

3)



where dashed lines indicate optional single or double bonds;

when R^a is ring M and ring M is aromatic, M^1 is carbon and is substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon and nitrogen and is unsubstituted or substituted with $(L)_nR^1$;

when ring M is partially saturated, M^1 is carbon and is mono- or di-substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon, nitrogen, oxygen and sulfur, and when M^2, M^3, M^4, or M^5 is oxygen or sulfur, it is unsubstituted, and when M^2, M^3, M^4 or M^6 is carbon or nitrogen, it is optionally unsubstituted; or mono- or di-substituted with $(L)_nR^1$;

when R^a is ring Q and ring Q is aromatic, Q^1 is selected from carbon and nitrogen, and when Q^1 is carbon, it is substituted with $(L)_nR^1$, and when Q^1 is nitrogen, it is unsubstituted, Q^4 is selected from nitrogen and carbon, and each of Q^2, Q^3 and Q^5 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

optionally when ring Q is aromatic, Q^1 is carbon and is substituted with $(L)_nR^1$, Q^4 is carbon, and one of Q^2, Q^3 and Q^5 is optionally oxygen or sulfur, and the remainder of Q^2, Q^3 and Q^5 are independently selected from nitrogen and carbon, and if carbon, are substituted with $(L)_nR^1$;

when ring Q is partially saturated, Q^1 is selected from carbon and nitrogen, and if carbon, it is mono- or di-substituted with $(L)_nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$, Q^4 is selected from carbon and nitrogen, but only one of Q^1 and Q^4 can be nitrogen, each of Q^2, Q^3 and Q^5 is independently selected from carbon, nitrogen, oxygen and sulfur, and if oxygen or sulfur, it is unsubstituted, and if carbon, it is mono- or di-substituted with $(L)nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$;

when R^a is structure 3, it is fully conjugated, X^2 is selected from oxygen or nitrogen substituted with $(L)_nR^1$, X^1 is carbon and is substituted with $(L)_nR^1$, and each of X^5 and X^6 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-R^{11}, C_2-C_8 alkenyl-R^{11}, C_2-C_8 alkynyl-R^{11}, C_1-C_8 alkyl-$(R^{11})_2$, C_2-C_8 alkenyl-$(R^{11})_2$, CSR^{11}, amino, $CONHR^{11}$, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NR^8R^9, (C_1-C_4)alkyl-$N(R^7)$-$N(R^8)(R^9)$, (C_1-C_4)alkyl$C(R^{11})$=N-$N(R^8)(R^9)$, (C_1-C_4)alkyl-N=$N(R^7)$, (C_1-C_4)alkyl-$N(R^7)$-N=$C(R^8)$, nitro, cyano, CO_2R^{11}, O-R^{10}, C_1-C_4 alkyl-OR^{10}, COR^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_8 alkyl-COR^{11}, C_1-C_8 alkyl-SR^{10}, C_1-C_8 alkyl-SOR^{11}, C_1-C_8 alkyl-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7, R^8 and R^9 are each independently selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_4 alkyl-R^{11}, C_1-C_8 alkyl-NHR^{13}, C_1-C_8 alkyl-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alkyl-OR^{15}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, $C(O)R^{17}$, $C(S)R^{17}$, $CONHR^{16}$, $C(S)NHR^{16}$, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SR^{15}, SOR^{17}, SO_2R^{17}, C_1-C_8 alkyl-CO_2R^{15}, C_1-C_8 alkyl-$C(S)OR^{15}$, C_1-C_8 alkyl-$C(O)SR^{15}$, C_1-C_8 alkyl-COR^{17}, C_1-C_8 alkyl-$C(S)R^{17}$, C_1-C_8 alkyl-$CONHR^{16}$, C_1-C_8 alkyl-$C(S)NHR^{16}$, C_1-C_8 alkyl-$CON(R^{16})_2$, C_1-C_8 alkyl-$C(S)N(R^{16})_2$, C_1-C_8 alkyl-SR^{15}, C_1-C_8 alkyl-SOR^{17}, C_1-C_8 alkyl-SO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{16};

R^{10} is selected from -H, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-NHR^{13}, C_1-C_8 alkyl-$NR^{13}R^{14}$, C_1-C_4 alkyl-OR^{15}, CSR^{11}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, COR^{17}, $C(S)R^{17}$, $CONHR^{16}$, C_1-C_4 alkyl-R^{11}, C_1-C_4

alkyl-NH_2R^{13}, C(S)NHR^{16}, O-R^{15}, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SOR^{17}, SO_2R^{17}, C_1-C_8 alkyl-CO_2R^{15}, C_1-C_8 alkyl-$C(S)OR^{15}$, C_1-C_8 alkyl-$C(O)SR^{15}$, C_1-C_8 alkyl-COR^{17}, C_1-C_8 alkyl-$C(S)R^{17}$, C_1-C_8 alkyl-$CONHR^{16}$, C_1-C_8 alkyl-$C(S)NHR^{16}$, C_1-C_8 alkyl-$CON(R^{16})_2$, $Si(R^{13})_2R^{17}$, C_1-C_8 alkyl-$C(S)N(R^{16})_2$, C_1-C_8 alkyl-SR^{15}, C_1-C_8 alkyl-SOR^{17}, C_1-C_8 alkyl-SO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, amino, NHR^{13}, $NR^{13}R^{14}$, $N{=}NR^{13}$, C_1-C_8 alkyl-NHR^{13}, C_1-C_8 alkyl-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alkyl-OR^{15}, SR^{15}, COR^{13}, CO_2R^{17}, C_1-C_8 alkyl-CO_2R^{15}, C_1-C_8 alkyl-$C(S)OR^{15}$, C_1-C_8 alkyl-$C(O)SR^{15}$, C_1-C_8 alkyl-COR^{17}, C_1-C_8 alkyl-$C(S)R^{17}$, C_1-C_8 alkyl-$CONHR^{16}$, C_1-C_8 alkyl-$C(S)NHR^{16}$, C_1-C_8 alkyl-$CON(R^{16})_2$, C_1-C_8 alkyl-$C(S)N(R^{16})_2$, C_1-C_8 alkyl-SR^{15}, C_1-C_8 alkyl-SOR^{17}, C_1-C_8 alkyl-SO_2R^{17}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, OH, oxo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{11}, C_2-C_{10} alkenyl-R^{11}, C_2-C_{10} alkynyl-R^{11}, C_1-C_{10} alkyl-$(R^{11})_2$, C_2-C_{10} alkenyl-$(R^{11})_2$, CSR^{11}, hydroxyl C_1-C_8 alkyl-R^{11}, amino C_1-C_4 alkyl-R^7, amino, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, $N{=}N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, $ON{=}C(R^{11})$, C_1-C_{10} alkyl-NHR^7, C_1-C_{10} alkyl-NR^8R^9, $(C_1$-$C_{10})$alkyl-$N(R^7)$-$N(R^8)(R^9)$, $(C_1$-$C_{10})$alkyl$C(R^{11})$=N-$N(R^8)(R^9)$, $(C_1$-$C_{10})$alkyl-N=$N(R^7)$, $(C_1$-$C_{10})$alkyl-$N(R^7)$-N=$C(R^8)$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-

R^{10}, C_1-C_{10} alkyl-OR^{10}, COR^{11}, CO_2R^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_{10} alkyl-COR^{11}, C_1-C_{10} alkyl-SR^{10}, C_1-C_{10} alkyl-SOR^{11}, C_1-C_{10} alkyl-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_4 alkyl-R^{23}, C_1-C_8 alkyl-NHR^{19}, C_1-C_8 alkyl-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alkyl-OR^{21}, CO_2R^{21}, COR^{21}, $C(S)OR^{21}$, $C(O)SR^{21}$, $C(O)R^{23}$, $C(S)R^{23}$, $CONHR^{22}$, $C(S)NHR^{22}$, $CON(R^{22})_2$, $C(S)N(R^{22})_2$, SR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_8 alkyl-CO_2R^{21}, C_1-C_8 alkyl-$C(S)OR^{21}$, C_1-C_8 alkyl-$C(O)SR^{21}$, C_1-C_8 alkyl-COR^{23}, C_1-C_8 alkyl-$C(S)R^{23}$, C_1-C_8 alkyl-$CONHR^{22}$, C_1-C_8 alkyl-$C(S)NHR^{22}$, C_1-C_8 alkyl-$CON(R^{22})_2$, C_1-C_8 alkyl-$C(S)N(R^{22})_2$, C_1-C_8 alkyl-SR^{21}, C_1-C_8 alkyl-SOR^{23}, C_1-C_8 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{15} and R^{16} are independently selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-NHR^{19}, C_1-C_8 alkyl-$NR^{19}R^{20}$, C_1-C_4 alkyl-OR^{21}, CSR^{11}, CO_2R^{22}, COR^{23}, $CONHR^{22}$, $CON(R^{22})_2$, SOR^{23}, SO_2R^{23}, C_1-C_8 alkyl-CO_2R^{22}, C_1-C_8 alkyl-COR^{23}, C_1-C_8 alkyl-$CONHR^{22}$, C_1-C_8 alkyl-$CON(R^{22})_2$, C_1-C_8 alkyl-SR^{21}, C_1-C_8 alkyl-SOR^{23}, C_1-C_8 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl,

heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkenyl-R^{19}, C_1-C_8 alkyl-R^{19}, C_2-C_8 alkynyl, amino, NHR^{19}, $NR^{19}R^{20}$, C_1-C_8 alkyl-NHR^{19}, C_1-C_8 alkyl-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alkyl-OR^{21}, SR^{21}, C_1-C_8 alkyl-CO_2R^{21}, C_1-C_8 alkyl-$C(S)OR^{21}$, C_1-C_8 alkyl-$C(O)SR^{21}$, C_1-C_8 alkyl-COR^{23}, C_1-C_8 alkyl-$C(S)R^{23}$, C_1-C_8 alkyl-$CONHR^{22}$, C_1-C_8 alkyl-$C(S)NHR^{22}$, C_1-C_8 alkyl-$CON(R^{22})_2$, C_1-C_8 alkyl-$C(S)N(R^{22})_2$, C_1-C_8 alkyl-SR^{21}, C_1-C_8 alkyl-SOR^{23}, C_1-C_8 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{23}, C_2-C_{10} alkenyl-R^{23}, C_2-C_{10} alkynyl-R^{23}, C_1-C_{10} alkyl-$(R^{23})_2$, C_2-C_{10} alkenyl-$(R^{23})_2$, CSR^{23}, amino, NHR^{19}, $NR^{20}R^{20}$, $N(R^{19})$-$N(R^{20})(R^{20})$, $C(R^{23})$=N-$N(R^{20})(R^{20})$, N=$N(R^{19})$, $N(R^{19})$-N=$C(R^{20})$, $C(R^{23})$=N-$O(R^{21})$, ON=$C(R^{23})$, C_1-C_{10} alkyl-NHR^{19}, C_1-C_{10} alkyl-$NR^{20}R^{20}$, (C_1-C_{10})alkyl-$N(R^{19})$-$N(R^{20})(R^{20})$, (C_1-C_{10})alkylC(R^{23})=N-$N(R^{20})(R^{20})$, (C_1-C_{10})alkyl-N=$N(R^{19})$, (C_1-C_{10})alkyl-$N(R^{19})$-N=$C(R^{20})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{21}, C_1-C_{10} alkyl-OR^{21}, COR^{23}, CO_2R^{23}, SR^{21}, SSR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_{10} alkyl-COR^{23}, C_1-C_{10} alkyl-SR^{21}, C_1-C_{10} alkyl-SOR^{23}, C_1-C_{10} alkyl-SO_2R^{23}, halo, $Si(R^{23})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl,

heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_4 alkyl-R^{29}, C_1-C_6 alkyl-NHR^{25}, C_1-C_6 alkyl-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alkyl-OR^{27}, CO_2R^{27}, $C(S)OR^{27}$, $C(O)SR^{27}$, $C(O)R^{29}$, $C(S)R^{29}$, $CONHR^{29}$, $C(S)NHR^{29}$, $CON(R^{25})_2$, $C(S)N(R^{25})_2$, SR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_6 alkyl-CO_2R^{27}, C_1-C_6 alkyl-$C(S)OR^{27}$, C_1-C_6 alkyl-$C(O)SR^{27}$, C_1-C_6 alkyl-COR^{29}, C_1-C_6 alkyl-$C(S)R^{29}$, C_1-C_6 alkyl-$CONHR^{29}$, C_1-C_6 alkyl-$C(S)NHR^{29}$, C_1-C_6 alkyl-$CON(R^{25})_2$, C_1-C_6 alkyl-$C(S)N(R^{25})_2$, C_1-C_6 alkyl-SR^{27}, C_1-C_6 alkyl-SOR^{29}, C_1-C_6 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are independently selected from -H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl-NHR^{25}, C_1-C_6 alkyl-$NR^{25}R^{26}$, C_1-C_4 alkyl-OR^{27}, CSR^{11}, CO_2R^{28}, COR^{29}, $CONHR^{29}$, $CON(R^{25})_2$, SOR^{29}, SO_2R^{29}, C_1-C_6 alkyl-CO_2R^{28}, C_1-C_6 alkyl-COR^{29}, C_1-C_6 alkyl-$CONHR^{29}$, C_1-C_6 alkyl-$CON(R^{25})_2$, C_1-C_6 alkyl-SR^{27}, C_1-C_6 alkyl-SOR^{29}, C_1-C_6 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{23} is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl-R^{25}, C_1-C_6 alkyl-R^{25}, C2-C_6 alkynyl, amino, NHR^{25}, $NR^{25}R^{26}$, C_1-C_6 alkyl-NHR^{25}, C_1-C_6 alkyl-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alkyl-OR^{27}, SR^{27}, C_1-C_6 alkyl-CO_2R^{27}, C_1-C_6 alkyl-$C(S)OR^{27}$, C_1-C_6 alkyl-$C(O)SR^{27}$, C_1-C_6 alkyl-COR^{29},

C_1-C_8 alkyl-C(S)R^{29}, C_1-C_8 alkyl-CONHR^{28}, C_1-C_8 alkyl-C(S)NHR^{28}, C_1-C_8 alkyl-CON(R^{28})$_2$, C_1-C_8 alkyl-C(S)N(R^{28})$_2$, C_1-C_8 alkyl-SR^{27}, C_1-C_8 alkyl-SOR^{29}, C_1-C_8 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{24} is selected from -H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{29}, C_2-C_{10} alkenyl-R^{29}, C_2-C_{10} alkynyl-R^{29}, C_1-C_{10} alkyl-(R^{29})$_2$, C_2-C_{10} alkenyl-(R^{29})$_2$, CSR^{29}, amino, NHR^{25}, N$R^{25}R^{26}$, N(R^{25})-N(R^{29})(R^{26}), C(R^{29})=N-N(R^{25})(R^{26}), N=N(R^{25}), N(R^{25})-N=C(R^{29}), C(R^{29})=N-O(R^{27}), ON=C(R^{29}), C_1-C_{10} alkyl-NHR^{25}, C_1-C_{10} alkyl-N$R^{25}R^{26}$, (C_1-C_{10})alkyl-N(R^{25})-N(R^{29})(R^{26}), (C_1-C_{10})alkylC(R^{29})=N-N(R^{29})(R^{26}), (C_1-C_{10})alkyl-N=N(R^{25}), (C_1-C_{10})alkyl-N(R^{25})-N=C(R^{29}), SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{27}, C_1-C_{10} alkyl-OR^{27}, CO_2R^{29}, COR^{29}, SR^{27}, SSR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_{10} alkyl-COR^{29}, C_1-C_{10} alkyl-SR^{27}, C_1-C_{10} alkyl-SOR^{29}, C_1-C_{10} alkyl-SO_2R^{29}, halo, Si(R^{29})$_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{25} and R^{26} are each independently selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_4 alkyl-R^{35}, C_1-C_8 alkyl-NHR^{31}, C_1-C_8 alkyl-N$R^{31}R^{32}$, O-R^{33}, C_1-C_4 alkyl-OR^{33}, CO_2R^{33}, C(S)OR^{33}, C(O)SR^{33}, C(O)R^{35}, C(S)R^{35}, CONHR^{34}, C(S)NHR^{34}, CON(R^{34})$_2$, C(S)N(R^{34})$_2$, SR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_8 alkyl-CO_2R^{33}, C_1-C_8 alkyl-C(S)OR^{33}, C_1-C_8 alkyl-C(O)SR^{33}, C_1-C_8 alkyl-COR^{35}, C_1-C_8 alkyl-C(S)R^{35}, C_1-C_8 alkyl-CONHR^{34}, C_1-C_8 alkyl-C(S)NHR^{34}, C_1-C_8 alkyl-CON(R^{34})$_2$, C_1-C_8 alkyl-C(S)N(R^{34})$_2$,

C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{38};

R^{27} and R^{28} are independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, C_1-C_4 alkyl-OR^{33}, CSR^{11}, CO_2R^{34}, COR^{35}, $CONHR^{34}$, $CON(R^{34})_2$, SOR^{35}, SO_2R^{35}, C_1-C_6 alkyl-CO_2R^{34}, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$CONHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{38};

R^{29} is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl-R^{31}, C_1-C_6 alkyl-R^{31}, C_2-C_6 alkynyl, amino, NHR^{31}, $NR^{31}R^{32}$, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alkyl-OR^{33}, SR^{33}, C_1-C_6 alkyl-CO_2R^{33}, C_1-C_6 alkyl-$C(S)OR^{33}$, C_1-C_6 alkyl-$C(O)SR^{33}$, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$C(S)R^{35}$, C_1-C_6 alkyl-$CONHR^{34}$, C_1-C_6 alkyl-$C(S)NHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-$C(S)N(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{38};

R^{30} is selected from -H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{35}, C_2-C_{10} alkenyl-R^{35}, C_2-C_{10} alkynyl-R^{35}, C_1-C_{10} alkyl-$(R^{35})_2$, C_2-C_{10} alkenyl-$(R^{35})_2$, CSR^{35}, amino, NHR^{31}, $NR^{32}R^{32}$, $N(R^{31})$-$N(R^{32})(R^{32})$, $C(R^{35})$=N-$N(R^{32})(R^{32})$, N=$N(R^{31})$, $N(R^{31})$-N=$C(R^{32})$, $C(R^{35})$=N-$O(R^{33})$, ON=$C(R^{35})$, C_1-C_{10} alkyl-NHR^{31}, C_1-C_{10} alkyl-$NR^{32}R^{32}$, (C_1-C_{10})alkyl-$N(R^{31})$-$N(R^{32})(R^{32})$, (C_1-C_{10})alkylC(R^{35})=N-$N(R^{32})(R^{32})$, (C_1-C_{10})alkyl-N=$N(R^{31})$, (C_1-C_{10})alkyl-$N(R^{31})$-N=$C(R^{32})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{33}, C_1-C_{10} alkyl-OR^{33}, COR^{35}, SR^{33}, SSR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_{10} alkyl-COR^{35}, C_1-C_{10} alkyl-SR^{33}, C_1-C_{10} alkyl-SOR^{35}, C_1-C_{10} alkyl-SO_2R^{35}, halo, $Si(R^{35})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{31}, R^{32}, R^{33} and R^{34} are each independently selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{35} is selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, OH, alkoxy, amino, alkylamino, dialkylamino, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic

cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{36} is selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, OH, alkoxy, amino, nitro, cyano, halo, alkylamino, dialkylamino, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heterocyclylalkyl, and heteroarylalkyl;

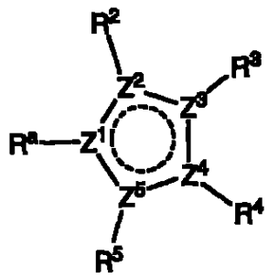
R^2, R^3, R^4, R^5, R^{37} and R^{38} are each independently absent, or selected from an R^1 group;

n is 0; and

R^3 and R^4 optionally join to form a ring of 5, 6, 7, or 8 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

[00014] The present invention is also directed to a novel compound having the structure of formula II:

Formula II.

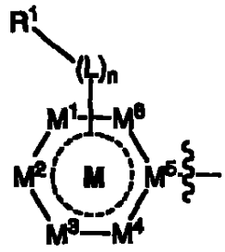


wherein:

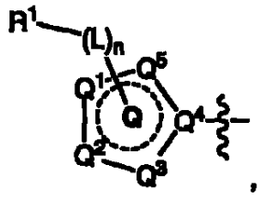
Z^2 and Z^3 are nitrogen, Z^1, Z^4 and Z^5 are carbon, and join with Z^2 and Z^3 to form a pyrazole ring, or optionally, Z^4 and Z^5 are nitrogen, Z^1, Z^2 and Z^3 are carbon and join with Z^4 and Z^5 to form a pyrazole ring;

R^8 is selected from:

1)

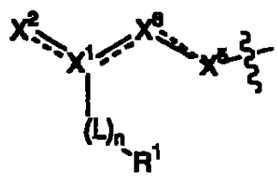


2)



, and

3)



where dashed lines indicate optional single or double bonds;

when R^a is ring M and ring M is aromatic, M^1 is carbon and is substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon and nitrogen and is unsubstituted or substituted with $(L)_nR^1$;

when ring M is partially saturated, M^1 is carbon and is mono- or di-substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon, nitrogen, oxygen and sulfur, and when M^2, M^3, M^4, or M^6 is oxygen or sulfur, it is unsubstituted, and when M^2, M^3, M^4 or M^6 is carbon or nitrogen, it is optionally unsubstituted; or mono- or di-substituted with $(L)_nR^1$;

when R^8 is ring Q and ring Q is aromatic, Q^1 is selected from carbon and nitrogen, and when Q^1 is carbon, it is substituted with $(L)_nR^1$, and when Q^1 is nitrogen, it is unsubstituted, Q^4 is selected from nitrogen and carbon, and each of Q^2, Q^3 and Q^5 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

optionally when ring Q is aromatic, Q^1 is carbon and is substituted with $(L)_nR^1$, Q^4 is carbon, and one of Q^2, Q^3 and Q^5 is optionally oxygen or sulfur, and the remainder of Q^2, Q^3 and Q^5 are independently selected from nitrogen and carbon, and if carbon, are substituted with $(L)_nR^1$;

when ring Q is partially saturated, Q^1 is selected from carbon and nitrogen, and if carbon, it is mono- or di-substituted with $(L)_nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$, Q^4 is selected from carbon and nitrogen, but only one of Q^1 and Q^4 can be nitrogen, each of Q^2, Q^3 and Q^5 is independently selected from carbon, nitrogen, oxygen and sulfur, and if oxygen or sulfur, it is unsubstituted, and if carbon, it is mono- or di-substituted with $(L)nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$;

when R^8 is structure 3, it is fully conjugated, X^2 is selected from oxygen or nitrogen substituted with $(L)_nR^1$, X^1 is carbon and is substituted with $(L)_nR^1$, and each of X^5 and X^6 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl-R^{11}, C_1-C_8 alkoxy-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^6)_2$, amino C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl-R^7, halo C_1-C_4 alkyl, C_1-C_8 alkyl-NHR^7, carbonitrile, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_8 alkyl, NR^8R^9-C_1-C_8 alkyl, nitro, cyano, O-R^{10}, C_1-C_4 alkyl-OR^{10}, C_1-C_8 alkyl-COR^{11}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7 and R^8 are each independently selected from -H, C_1-C_8 alkyl, C_1-C_4 alkyl-R^{11}, C_1-C_8 alkyl-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, aryl, and arylalkyl, wherein aryl and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^9 and R^{10} are each independently selected from -H, hydroxyl, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{17}, C_1-C_8 alkyl-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_8 alkyl-CO_2R^{16}, C_1-C_8 alkyl-$CONH$-R^{16}, C_1-C_8 alkyl-$CON(R^{16})_2$, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkoxy, halo C_1-C_4 alkyl, $Si(R^{13})_2R^{17}$, aryl, heteroaryl, heterocyclyl, arylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxyl, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, wherein heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, hydroxyl, oxo, C_1-C_8 alkyl, hydroxyl C_1-C_8 alkyl-R^{11}, C_1-C_{10} alkoxy, amino, amino C_1-C_4 alkyl-R^7, NHR^7, $N(R^7)_2$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NHR^8R^9, C_1-C_8 alkyl-$N(R^8)_2$, C_1-C_8 alkyl-R^{11}, C_1-C_8 alkyl-$CO_2R^7R^{11}$, C_1-C_8 alkoxy-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_8 alkyl-SR^{10}, halo, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, COR^{23}, and aryl;

R^{15} and R^{19} are each independently selected from -H, aryl, arylalkyl, wherein aryl, arylalkyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{19}, NHR^{19}, aryl, heteroarylalkyl, and heterocyclylalkyl, wherein aryl is optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, hydroxyl, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, amino, amino C_1-C_8 alkyl, $N(R^{19})_2$, C_1-C_8 alkyl-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, heteroaryl, heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are each independently selected from –H and C_1-C_8 alkyl;

R^{23} is selected from –H and C_1-C_8 alkyl;

R^{24} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, CO_2R^{29}, halo, and halo C_1-C_4 alkyl;

R^{29} is selected from -H, and C_1-C_8 alkyl;

R^{30} is selected from -H, aryl, heteroaryl, heterocyclyl, alkylaryl, arylalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{36};

R^{36} is selected from –H and halo;

R^2, R^3, R^4, R^{37} and R^{38} are each independently selected from an R^1 group;

n is 0; and

R^3 and R^4 optionally join to form a ring of 5, 6, 7, or 8 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

[00015] The present invention is also directed to a novel MK-2 inhibiting compound that is listed in Table I or Table II, below.

[00016] The present invention is also directed to a novel method of inhibiting MK-2, the method comprising contacting MK-2 with at least one compound that is described in Table I or Table II, below.

[00017] The present invention is also directed to a novel method of preventing or treating a TNFα mediated disease or disorder in a subject, the method comprising administering to the subject an effective amount of an MK-2 inhibiting compound having the structure described in formula I.

[00018] The present invention is also directed to a novel method of preventing or treating a TNFα mediated disease or disorder in a subject, the method comprising administering to the subject at least one MK-2 inhibiting compound that is described in Table I or Table II, below.

[00019] The present invention is also directed to a novel therapeutic composition comprising a compound having the structure described in formula I.

[00020] The present invention is also directed to a novel therapeutic composition comprising at least one MK-2 inhibitory compound that is described in Table I or Table II.

[00021] The present invention is also directed to a novel pharmaceutical composition comprising a pharmaceutically acceptable carrier.and at least one MK-2 inhibitory compound having the structure described in formula I.

[00022] The present invention is also directed to a novel comprising a dosage form that includes a therapeutically effective amount of at least one MK-2 inhibitory compound having a structure described in formula I.

[00023] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of a method that could serve to modulate the activity of MK-2 – in particular, to inhibit MK-2 activity – and the provision of a method for the prevention and treatment of diseases and disorders that are mediated by TNFα.

BRIEF DESCRIPTION OF THE DRAWINGS

[00024] Figure 1 is a graph showing paw thickness as a function of time from day 0 to day 7 for MK2 (+/+) and MK2 (-/-) mice, which have received serum injection; and

[00025] Figure 2 is a bar chart showing paw thickness at seven days after injection for normal mice, MK2 (+/+) mice receiving serum, MK2 (-/-) mice receiving serum, and MK2 (+/+) mice receiving serum and anti-TNF antibody;

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00026] In accordance with the present invention, it has been discovered that certain compounds can inhibit the activity of MAPKAP kinase-2. Many of these compounds exhibit their inhibitory effect at low concentrations – having *in vitro* MK-2 inhibition IC_{50} values of under 1.0 μM, and with some having IC_{50} values of under about 0.1 μM, and even as low as about 0.02 μM. Accordingly, these compounds can be potent and effective drugs for use in the inhibition of MK-2, and of special value in subjects where such inhibition would be useful. In particular, these compounds would be useful in methods to prevent or treat diseases and disorders that are mediated by TNFα. For example, they can be used for the prevention or treatment of arthritis.

[00027] Compounds that have a high degree of MK-2 inhibiting activity offer advantages in therapeutic uses, because therapeutic benefits can be obtained by the administration of lower amounts of the present compounds than with less active compounds. Such highly active compounds also result in fewer side effects, and in some embodiments, demonstrate a selectivity for MK-2 inhibition over the inhibition of other related kinases.

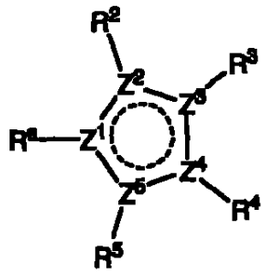
[00028] The present MK-2 inhibitory compounds inhibit the activity of the MK-2 enzyme. When it is said that a subject compound inhibits MK-2, it is meant that the MK-2 enzymatic activity is lower in the presence of the compound than it is under the same conditions in the absence of such compound. One method of expressing the potency of a compound as an MK-2 inhibitor is to measure the "IC_{50}" value of the compound. The IC_{50} value of an MK-2 inhibitor is the concentration of the compound that is required to decrease the MK-2 enzymatic activity by one-half. Accordingly, a compound having a lower IC_{50} value is considered to be a more potent inhibitor than a compound having a higher IC_{50} value. As

used herein, compounds that inhibit MK-2 can be referred to as MK-2 inhibitors, or MK-2 inhibiting compounds or MK-2 inhibiting agents.

[00029] In practice, the selectivity of an MK-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of an MK-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of MK-3, divided by the IC_{50} value for inhibition of MK-2 ($IC_{50\ MK-3}/IC_{50\ MK-2}$). As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of MK-2 or MK-3 activity. An MK-2 selective inhibitor is any inhibitor for which the ratio of $IC_{50\ MK-3}$ to $IC_{50\ MK-2}$ is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still, is greater than 100. Such preferred selectivity may indicate an ability to reduce the incidence of side effects incident to the administration of an MK-2 inhibitor to a subject.

[00030] Compounds that are useful in the present method include those having the structure shown in formula I:

Formula I:

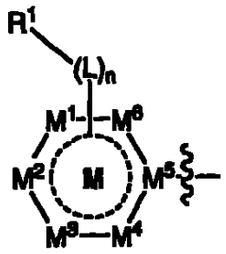


wherein:

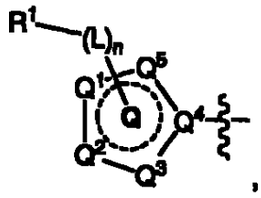
Z^2 and Z^3 are nitrogen, Z^1, Z^4 and Z^5 are carbon, and join with Z^2 and Z^3 to form a pyrazole ring, or optionally, Z^4 and Z^5 are nitrogen, Z^1, Z^2 and Z^3 are carbon and join with Z^4 and Z^5 to form a pyrazole ring;

R^1 is selected from:

1)

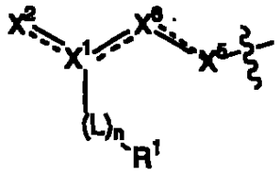


2)



, and

3)



where dashed lines indicate optional single or double bonds;

when R^6 is ring M and ring M is aromatic, M^1 is carbon and is substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon and nitrogen and is unsubstituted or substituted with $(L)_nR^1$;

when ring M is partially saturated, M^1 is carbon and is mono- or di-substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon, nitrogen, oxygen and sulfur, and when M^2, M^3, M^4, or M^6 is oxygen or sulfur, it is unsubstituted, and when M^2, M^3, M^4 or M^6 is carbon or nitrogen, it is optionally unsubstituted; or mono- or di-substituted with $(L)_nR^1$;

when R^8 is ring Q and ring Q is aromatic, Q^1 is selected from carbon and nitrogen, and when Q^1 is carbon, it is substituted with $(L)_nR^1$, and when Q^1 is nitrogen, it is unsubstituted, Q^4 is selected from nitrogen and carbon, and each of Q^2, Q^3 and Q^5 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

optionally when ring Q is aromatic, Q^1 is carbon and is substituted with $(L)_nR^1$, Q^4 is carbon, and one of Q^2, Q^3 and Q^5 is optionally oxygen or sulfur, and the remainder of Q^2, Q^3 and Q^5 are independently selected from nitrogen and carbon, and if carbon, are substituted with $(L)_nR^1$;

when ring Q is partially saturated, Q^1 is selected from carbon and nitrogen, and if carbon, it is mono- or di-substituted with $(L)_nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$, Q^4 is selected from carbon and nitrogen, but only one of Q^1 and Q^4 can be nitrogen, each of Q^2, Q^3 and Q^5 is independently selected from carbon, nitrogen, oxygen and sulfur, and if oxygen or sulfur, it is unsubstituted, and if carbon, it is mono- or di-substituted with (L)nR^1, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$;

when R^8 is structure 3, it is fully conjugated, X^2 is selected from oxygen or nitrogen substituted with $(L)_nR^1$, X^1 is carbon and is substituted with $(L)_nR^1$, and each of X^5 and X^6 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-R^{11}, C_2-C_8 alkenyl-R^{11}, C_2-C_8 alkynyl-R^{11}, C_1-C_8 alkyl-$(R^{11})_2$, C_2-C_8 alkenyl-$(R^{11})_2$, CSR^{11}, amino, $CONHR^{11}$, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NR^8R^9, (C_1-C_4)alkyl-$N(R^7)$-$N(R^8)(R^9)$, (C_1-C_4)alkyl$C(R^{11})$=N-$N(R^8)(R^9)$, (C_1-C_4)alkyl-N=$N(R^7)$, (C_1-C_4)alkyl-$N(R^7)$-N=$C(R^8)$, nitro, cyano, CO_2R^{11}, O-R^{10}, C_1-C_4 alkyl-OR^{10}, COR^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_8 alkyl-COR^{11}, C_1-C_8 alkyl-SR^{10}, C_1-C_8 alkyl-SOR^{11}, C_1-C_8 alkyl-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic

cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7, R^8 and R^9 are each independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_4 alkyl-R^{11}, C_1-C_6 alkyl-NHR^{13}, C_1-C_6 alkyl-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alkyl-OR^{15}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, $C(O)R^{17}$, $C(S)R^{17}$, $CONHR^{16}$, $C(S)NHR^{16}$, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SR^{15}, SOR^{17}, SO_2R^{17}, C_1-C_6 alkyl-CO_2R^{15}, C_1-C_6 alkyl-$C(S)OR^{15}$, C_1-C_6 alkyl-$C(O)SR^{15}$, C_1-C_6 alkyl-COR^{17}, C_1-C_6 alkyl-$C(S)R^{17}$, C_1-C_6 alkyl-$CONHR^{16}$, C_1-C_6 alkyl-$C(S)NHR^{16}$, C_1-C_6 alkyl-$CON(R^{16})_2$, C_1-C_6 alkyl-$C(S)N(R^{16})_2$, C_1-C_6 alkyl-SR^{15}, C_1-C_6 alkyl-SOR^{17}, C_1-C_6 alkyl-SO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{10} is selected from -H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl-NHR^{13}, C_1-C_6 alkyl-$NR^{13}R^{14}$, C_1-C_4 alkyl-OR^{15}, CSR^{11}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, COR^{17}, $C(S)R^{17}$, $CONHR^{16}$, C_1-C_4 alkyl-R^{11}, C_1-C_4 alkyl-NH_2R^{13}, $C(S)NHR^{16}$, O-R^{15}, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SOR^{17}, SO_2R^{17}, C_1-C_6 alkyl-CO_2R^{15}, C_1-C_6 alkyl-$C(S)OR^{15}$, C_1-C_6 alkyl-$C(O)SR^{15}$, C_1-C_6 alkyl-COR^{17}, C_1-C_6 alkyl-$C(S)R^{17}$, C_1-C_6 alkyl-$CONHR^{16}$, C_1-C_6 alkyl-$C(S)NHR^{16}$, C_1-C_6 alkyl-$CON(R^{16})_2$, $Si(R^{13})_2R^{17}$, C_1-C_6 alkyl-$C(S)N(R^{16})_2$, C_1-C_6 alkyl-SR^{15}, C_1-C_6 alkyl-SOR^{17}, C_1-C_6 alkyl-SO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, amino, NHR^{13}, $NR^{13}R^{14}$, $N{=}NR^{13}$, C_1-C_8 alkyl-NHR^{13}, C_1-C_8 alkyl-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alkyl-OR^{15}, SR^{15}, COR^{13}, CO_2R^{17}, C_1-C_8 alkyl-CO_2R^{15}, C_1-C_8 alkyl-$C(S)OR^{15}$, C_1-C_8 alkyl-$C(O)SR^{15}$, C_1-C_8 alkyl-COR^{17}, C_1-C_8 alkyl-$C(S)R^{17}$, C_1-C_8 alkyl-$CONHR^{16}$, C_1-C_8 alkyl-$C(S)NHR^{16}$, C_1-C_8 alkyl-$CON(R^{16})_2$, C_1-C_8 alkyl-$C(S)N(R^{16})_2$, C_1-C_8 alkyl-SR^{15}, C_1-C_8 alkyl-SOR^{17}, C_1-C_8 alkyl-SO_2R^{17}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, OH, oxo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{11}, C_2-C_{10} alkenyl-R^{11}, C_2-C_{10} alkynyl-R^{11}, C_1-C_{10} alkyl-$(R^{11})_2$, C_2-C_{10} alkenyl-$(R^{11})_2$, CSR^{11}, hydroxyl C_1-C_8 alkyl-R^{11}, amino C_1-C_4 alkyl-R^7, amino, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, $N{=}N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_{10} alkyl-NHR^7, C_1-C_{10} alkyl-NR^8R^9, (C_1-C_{10})alkyl-$N(R^7)$-$N(R^8)(R^9)$, (C_1-C_{10})alkylC(R^{11})=N-$N(R^8)(R^9)$, (C_1-C_{10})alkyl-N=$N(R^7)$, (C_1-C_{10})alkyl-$N(R^7)$-N=$C(R^8)$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{10}, C_1-C_{10} alkyl-OR^{10}, COR^{11}, CO_2R^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_{10} alkyl-COR^{11}, C_1-C_{10} alkyl-SR^{10}, C_1-C_{10} alkyl-SOR^{11}, C_1-C_{10} alkyl-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_4 alkyl-R^{23}, C_1-C_8 alkyl-NHR^{16}, C_1-

C_8 alkyl-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alkyl-OR^{21}, CO_2R^{21}, COR^{21}, $C(S)OR^{21}$, $C(O)SR^{21}$, $C(O)R^{23}$, $C(S)R^{23}$, $CONHR^{22}$, $C(S)NHR^{22}$, $CON(R^{22})_2$, $C(S)N(R^{22})_2$, SR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_8 alkyl-CO_2R^{21}, C_1-C_8 alkyl-$C(S)OR^{21}$, C_1-C_8 alkyl-$C(O)SR^{21}$, C_1-C_8 alkyl-COR^{23}, C_1-C_8 alkyl-$C(S)R^{23}$, C_1-C_8 alkyl-$CONHR^{22}$, C_1-C_8 alkyl-$C(S)NHR^{22}$, C_1-C_8 alkyl-$CON(R^{22})_2$, C_1-C_8 alkyl-$C(S)N(R^{22})_2$, C_1-C_8 alkyl-SR^{21}, C_1-C_8 alkyl-SOR^{23}, C_1-C_8 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{15} and R^{16} are independently selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-NHR^{19}, C_1-C_8 alkyl-$NR^{19}R^{20}$, C_1-C_4 alkyl-OR^{21}, CSR^{11}, CO_2R^{22}, COR^{23}, $CONHR^{22}$, $CON(R^{22})_2$, SOR^{23}, SO_2R^{23}, C_1-C_8 alkyl-CO_2R^{22}, C_1-C_8 alkyl-COR^{23}, C_1-C_8 alkyl-$CONHR^{22}$, C_1-C_8 alkyl-$CON(R^{22})_2$, C_1-C_8 alkyl-SR^{21}, C_1-C_8 alkyl-SOR^{23}, C_1-C_8 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkenyl-R^{19}, C_1-C_8 alkyl-R^{19}, C_2-C_8 alkynyl, amino, NHR^{19}, $NR^{19}R^{20}$, C_1-C_8 alkyl-NHR^{19}, C_1-C_8 alkyl-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alkyl-OR^{21}, SR^{21}, C_1-C_8 alkyl-CO_2R^{21}, C_1-C_8 alkyl-$C(S)OR^{21}$, C_1-C_8 alkyl-$C(O)SR^{21}$, C_1-C_8 alkyl-COR^{23}, C_1-C_8 alkyl-$C(S)R^{23}$, C_1-C_8 alkyl-$CONHR^{22}$, C_1-C_8 alkyl-$C(S)NHR^{22}$, C_1-C_8 alkyl-$CON(R^{22})_2$, C_1-C_8 alkyl-$C(S)N(R^{22})_2$, C_1-C_8 alkyl-SR^{21}, C_1-C_8 alkyl-SOR^{23}, C_1-C_8 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl,

alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{23}, C_2-C_{10} alkenyl-R^{23}, C_2-C_{10} alkynyl-R^{23}, C_1-C_{10} alkyl-$(R^{23})_2$, C_2-C_{10} alkenyl-$(R^{23})_2$, CSR^{23}, amino, NHR^{19}, $NR^{20}R^{20}$, $N(R^{19})$-$N(R^{20})(R^{20})$, $C(R^{23})$=N-$N(R^{20})(R^{20})$, N=$N(R^{19})$, $N(R^{19})$-N=$C(R^{20})$, $C(R^{23})$=N-$O(R^{21})$, ON=$C(R^{23})$, C_1-C_{10} alkyl-NHR^{19}, C_1-C_{10} alkyl-$NR^{20}R^{20}$, (C_1-C_{10})alkyl-$N(R^{19})$-$N(R^{20})(R^{20})$, (C_1-C_{10})alkyl$C(R^{23})$=N-$N(R^{20})(R^{20})$, (C_1-C_{10})alkyl-N=$N(R^{19})$, (C_1-C_{10})alkyl-$N(R^{19})$-N=$C(R^{20})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{21}, C_1-C_{10} alkyl-OR^{21}, COR^{23}, CO_2R^{23}, SR^{21}, SSR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_{10} alkyl-COR^{23}, C_1-C_{10} alkyl-SR^{21}, C_1-C_{10} alkyl-SOR^{23}, C_1-C_{10} alkyl-SO_2R^{23}, halo, $Si(R^{23})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_4 alkyl-R^{29}, C_1-C_8 alkyl-NHR^{25}, C_1-C_8 alkyl-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alkyl-OR^{27}, CO_2R^{27}, $C(S)OR^{27}$, $C(O)SR^{27}$, $C(O)R^{29}$, $C(S)R^{29}$, $CONHR^{25}$, $C(S)NHR^{25}$, $CON(R^{25})_2$, $C(S)N(R^{25})_2$, SR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_8 alkyl-CO_2R^{27}, C_1-C_8 alkyl-$C(S)OR^{27}$, C_1-C_8 alkyl-$C(O)SR^{27}$, C_1-C_8 alkyl-COR^{29}, C_1-C_8 alkyl-$C(S)R^{29}$, C_1-C_8 alkyl-$CONHR^{25}$, C_1-C_8 alkyl-$C(S)NHR^{25}$, C_1-C_8 alkyl-$CON(R^{25})_2$, C_1-C_8 alkyl-$C(S)N(R^{25})_2$, C_1-C_8 alkyl-SR^{27}, C_1-C_8 alkyl-SOR^{29}, C_1-C_8 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic

cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are independently selected from -H, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-NHR^{25}, C_1-C_8 alkyl-$NR^{25}R^{26}$, C_1-C_4 alkyl-OR^{27}, CSR^{11}, CO_2R^{28}, COR^{29}, $CONHR^{26}$, $CON(R^{25})_2$, SOR^{29}, SO_2R^{29}, C_1-C_8 alkyl-CO_2R^{28}, C_1-C_8 alkyl-COR^{29}, C_1-C_8 alkyl-$CONHR^{26}$, C_1-C_8 alkyl-$CON(R^{25})_2$, C_1-C_8 alkyl-SR^{27}, C_1-C_8 alkyl-SOR^{29}, C_1-C_8 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{23} is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkenyl-R^{25}, C_1-C_8 alkyl-R^{25}, C2-C_8 alkynyl, amino, NHR^{25}, $NR^{25}R^{26}$, C_1-C_8 alkyl-NHR^{25}, C_1-C_8 alkyl-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alkyl-OR^{27}, SR^{27}, C_1-C_8 alkyl-CO_2R^{27}, C_1-C_8 alkyl-$C(S)OR^{27}$, C_1-C_8 alkyl-$C(O)SR^{27}$, C_1-C_8 alkyl-COR^{29}, C_1-C_8 alkyl-$C(S)R^{29}$, C_1-C_8 alkyl-$CONHR^{26}$, C_1-C_8 alkyl-$C(S)NHR^{26}$, C_1-C_8 alkyl-$CON(R^{25})_2$, C_1-C_8 alkyl-$C(S)N(R^{25})_2$, C_1-C_8 alkyl-SR^{27}, C_1-C_8 alkyl-SOR^{29}, C_1-C_8 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{24} is selected from -H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{29}, C_2-C_{10} alkenyl-R^{29}, C_2-C_{10} alkynyl-R^{29}, C_1-C_{10} alkyl-$(R^{29})_2$, C_2-C_{10} alkenyl-$(R^{29})_2$, CSR^{29}, amino, NHR^{25}, $NR^{25}R^{26}$, $N(R^{25})$-

$N(R^{25})(R^{25})$, $C(R^{25})=N-N(R^{25})(R^{25})$, $N=N(R^{25})$, $N(R^{25})-N=C(R^{25})$, $C(R^{25})=N-O(R^{27})$, $ON=C(R^{25})$, C_1-C_{10} alkyl-NHR^{25}, C_1-C_{10} alkyl-$NR^{25}R^{25}$, (C_1-C_{10})alkyl-$N(R^{25})-N(R^{25})(R^{25})$, ($C_1$-$C_{10}$)alkyl$C(R^{25})=N-N(R^{25})(R^{25})$, ($C_1$-$C_{10}$)alkyl-$N=N(R^{25})$, ($C_1$-$C_{10}$)alkyl-$N(R^{25})-N=C(R^{25})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{27}, C_1-C_{10} alkyl-OR^{27}, CO_2R^{28}, COR^{29}, SR^{27}, SSR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_{10} alkyl-COR^{29}, C_1-C_{10} alkyl-SR^{27}, C_1-C_{10} alkyl-SOR^{29}, C_1-C_{10} alkyl-SO_2R^{29}, halo, $Si(R^{29})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{25} and R^{26} are each independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_4 alkyl-R^{35}, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alkyl-OR^{33}, CO_2R^{33}, $C(S)OR^{33}$, $C(O)SR^{33}$, $C(O)R^{35}$, $C(S)R^{35}$, $CONHR^{34}$, $C(S)NHR^{34}$, $CON(R^{34})_2$, $C(S)N(R^{34})_2$, SR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_6 alkyl-CO_2R^{33}, C_1-C_6 alkyl-$C(S)OR^{33}$, C_1-C_6 alkyl-$C(O)SR^{33}$, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$C(S)R^{35}$, C_1-C_6 alkyl-$CONHR^{34}$, C_1-C_6 alkyl-$C(S)NHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-$C(S)N(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{27} and R^{28} are independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, C_1-C_4 alkyl-OR^{33}, CSR^{11}, CO_2R^{34}, COR^{35}, $CONHR^{34}$, $CON(R^{34})_2$, SOR^{35}, SO_2R^{35}, C_1-C_6 alkyl-CO_2R^{34}, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$CONHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-

SO_2R^{36}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{29} is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl-R^{31}, C_1-C_6 alkyl-R^{31}, C_2-C_6 alkynyl, amino, NHR^{31}, $NR^{31}R^{32}$, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alkyl-OR^{33}, SR^{33}, C_1-C_6 alkyl-CO_2R^{33}, C_1-C_6 alkyl-$C(S)OR^{33}$, C_1-C_6 alkyl-$C(O)SR^{33}$, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$C(S)R^{35}$, C_1-C_6 alkyl-$CONHR^{34}$, C_1-C_6 alkyl-$C(S)NHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-$C(S)N(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{30} is selected from -H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{35}, C_2-C_{10} alkenyl-R^{35}, C_2-C_{10} alkynyl-R^{35}, C_1-C_{10} alkyl-$(R^{35})_2$, C_2-C_{10} alkenyl-$(R^{35})_2$, CSR^{35}, amino, NHR^{31}, $NR^{32}R^{32}$, $N(R^{31})$-$N(R^{32})(R^{32})$, $C(R^{35})$=N-$N(R^{32})(R^{32})$, N=$N(R^{31})$, $N(R^{31})$-N=$C(R^{32})$, $C(R^{35})$=N-$O(R^{33})$, ON=$C(R^{35})$, C_1-C_{10} alkyl-NHR^{31}, C_1-C_{10} alkyl-$NR^{32}R^{32}$, (C_1-C_{10})alkyl-$N(R^{31})$-$N(R^{32})(R^{32})$, (C_1-C_{10})alkylC(R^{35})=N-$N(R^{32})(R^{32})$, (C_1-C_{10})alkyl-N=$N(R^{31})$, (C_1-C_{10})alkyl-$N(R^{31})$-N=$C(R^{32})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{33}, C_1-C_{10} alkyl-OR^{33}, COR^{35}, SR^{33}, SSR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_{10} alkyl-COR^{35}, C_1-C_{10} alkyl-SR^{33}, C_1-C_{10} alkyl-SOR^{35}, C_1-C_{10} alkyl-SO_2R^{35}, halo, $Si(R^{35})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10}

mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{31}, R^{32}, R^{33} and R^{34} are each independently selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{35};

R^{35} is selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, OH, alkoxy, amino, alkylamino, dialkylamino, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{36} is selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, OH, alkoxy, amino, nitro, cyano, halo, alkylamino, dialkylamino, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heterocyclylalkyl, and heteroarylalkyl;

R^2, R^3, R^4, R^5, R^{37} and R^{38} are each independently absent, or selected from an R^1 group;

n is 0; and

R^3 and R^4 optionally join to form a ring of 5, 6, 7, or 8 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, O, S, C=O,

C=S, S=O, SO_2, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

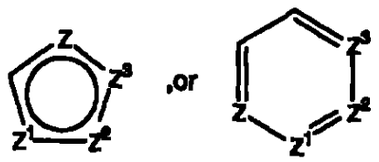
[00031] The "M" ring and the "Q" ring of the structure of formula I can have any number of R^1-L_n- substituent groups, ranging from zero to one or more per ring atom, and such substituent groups can be located on any atom of the ring having a valence suitable for the addition of a substituent group(s). Each such substituent group can have any number of R^1 groups per L group, ranging from zero to 5. A preferred structure is the presence of either 0 or 1 R^1-L_n- substituent groups on the ring. It is also preferred that the R^1-L_n- substituent group is attached to the ring at the M^1 or the Q^1 location, respectively.

[00032] The meaning of any substituent at any one occurrence in Formula I, or any other general chemical formula herein, is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

[00033] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The number of carbon atoms can also be expressed as "C_1-C_5", for example. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like. The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. Unless otherwise noted, such radicals preferably contain from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-

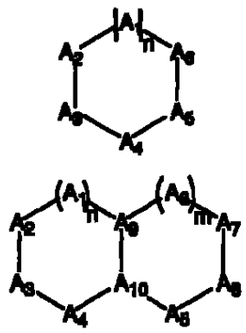
hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like. The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups as described below. Examples of suitable alkynyl radicals include ethynyl, proynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like. The term "oxo" means a single double-bonded oxygen. The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical. The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. Likewise, the term "halo", when it is appended to alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heteroaryl, and the like, includes radicals having mono-, di-, or tri-, halo substitution on one or more of the atoms of the radical. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy

radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy. Terms such as "alkoxy(halo)alkyl", indicate a molecule having a terminal alkoxy that is bound to an alkyl, which is bonded to the parent molecule, while the alkyl also has a substituent halo group in a non-terminal location. In other words, both the alkoxy and the halo group are substituents of the alkyl chain. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl. The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also

termed "heteroaryl" radicals include thienyl, pyrryl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The terms aryl or heteroaryl, as appropriate, include the following structures:



where:

when n=1, m=1 and A_1-A_8 are each CR^x or N, A_9 and A_{10} are carbon;

when n=0, or 1, and m=0, or 1, one of A_2-A_4 and/or A_5-A_7 is optionally S, O, or NR^x, and other ring members are CR^x or N, with the proviso that oxygen cannot be adjacent to sulfur in a ring. A_9 and A_{10} are carbon;

when n is greater than or equal to 0, and m is greater than or equal to 0, 1 or more sets of 2 or more adjacent atoms A_1-A_{10} are sp3 O, S, NR^x, CR^xR^y, or C=(O or S), with the proviso that oxygen and sulfur cannot be adjacent. The remaining A_1-A_8 are CR^x or N, and A_9 and A_{10} are carbon;

when n is greater than or equal to 0, and m greater than or equal to 0, atoms separated by 2 atoms (*i.e.*, A_1 and A_4) are Sp3 O, S, NR^x, CR^xR^y, and remaining A_1-A_8 are independently CR^x or N, and A_9 and A_{10} are carbon.

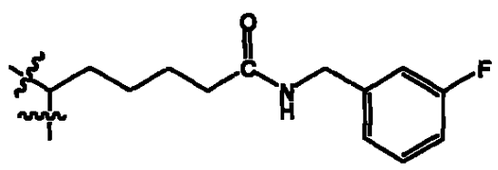
[00034] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical,

where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2-NH_2$), which may also be termed an "aminosulfonyl". The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2-H$. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes – (C=O) –. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3 – (CO) –. The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3-C-O-C=O)$ – and – (O=)C– OCH_3. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such "alkoxycarbonylalkyl" radicals include $(CH_3)_3C-OC(=O)-(CH_2)_2$ – and – $(CH_2)_2$ (–O)$COCH_3$. The terms "amido", or "carbamyl", when used alone or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with

one alkylradical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkylradicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an –C(–NH)–NH_2 radical. The term "cyanoamidin" denotes an –C(–N–CN) –NH_2 radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The terms "aralkyl", or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3 –S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(–O) – atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino"

embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino (CH_3-C(=O) –NH–).

[00035] In the naming of substituent groups for general chemical structures, the naming of the chemical components of the group is typically from the terminal group-toward the parent compound unless otherwise noted, as discussed below. In other words, the outermost chemical structure is named first, followed by the next structure in line, followed by the next, etc. until the structure that is connected to the parent structure is named. For example, a substituent group having a structure such as:

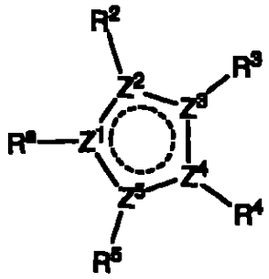


may be referred to generally as a "haloarylalkylaminocarboxylalkyl". An example of one such group would be fluorophenylmethylcarbamylpentyl. The bonds having wavy lines through them represent the parent structure to which the alkyl is attached.

[00036] Substituent groups may also be named by reference to one or more "R" groups. The structure shown above would be included in a description, such as, "-C_1-C_6-alkyl-COR^U, where R^U is defined to include -NH-C_1-C_4-alkylaryl-R^V, and where R^V is defined to include halo. In this scheme, atoms having an "R" group are shown with the "R" group being the terminal group (*i.e.*, furthest from the parent). In a term such as "$C(R^X)_2$", it should be understood that the two R^X groups can be the same, or they can be different if R^X is defined as having more than one possible identity.

[00037] The present invention also comprises MK-2 inhibiting compounds having the structure shown in formula II:

Formula II.

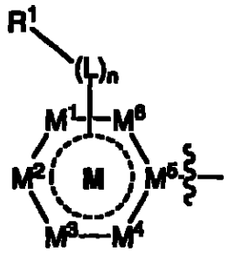


wherein:

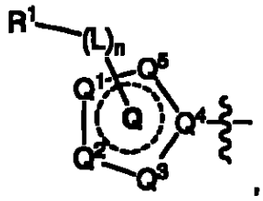
Z^2 and Z^3 are nitrogen, Z^1, Z^4 and Z^5 are carbon, and join with Z^2 and Z^3 to form a pyrazole ring, or optionally, Z^4 and Z^5 are nitrogen, Z^1, Z^2 and Z^3 are carbon and join with Z^4 and Z^5 to form a pyrazole ring;

R^a is selected from:

1)

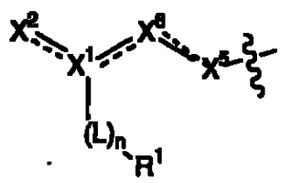


2)



, and

3)



where dashed lines indicate optional single or double bonds;

when R^a is ring M and ring M is aromatic, M^1 is carbon and is substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon and nitrogen and is unsubstituted or substituted with $(L)_nR^1$;

when ring M is partially saturated, M^1 is carbon and is mono- or di-substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon, nitrogen, oxygen and sulfur, and when M^2, M^3, M^4, or M^6 is oxygen or sulfur, it is unsubstituted, and when M^2, M^3, M^4 or M^6 is carbon or nitrogen, it is optionally unsubstituted; or mono- or di-substituted with $(L)_nR^1$;

when R^a is ring Q and ring Q is aromatic, Q^1 is selected from carbon and nitrogen, and when Q^1 is carbon, it is substituted with $(L)_nR^1$, and when Q^1 is nitrogen, it is unsubstituted, Q^4 is selected from nitrogen and carbon, and each of Q^2, Q^3 and Q^5 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

optionally when ring Q is aromatic, Q^1 is carbon and is substituted with $(L)_nR^1$, Q^4 is carbon, and one of Q^2, Q^3 and Q^5 is optionally oxygen or sulfur, and the remainder of Q^2, Q^3 and Q^5 are independently selected from nitrogen and carbon, and if carbon, are substituted with $(L)_nR^1$;

when ring Q is partially saturated, Q^1 is selected from carbon and nitrogen, and if carbon, it is mono- or di-substituted with $(L)_nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$, Q^4 is selected from carbon and nitrogen, but only one of Q^1 and Q^4 can be nitrogen, each of Q^2, Q^3 and Q^5 is independently selected from carbon, nitrogen, oxygen and sulfur, and if oxygen or sulfur, it is unsubstituted, and if carbon, it is mono- or di-substituted with $(L)nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$;

when R^a is structure 3, it is fully conjugated, X^2 is selected from oxygen or nitrogen substituted with $(L)_nR^1$, X^1 is carbon and is substituted with $(L)_nR^1$, and each of X^5 and X^6 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl-R^{11}, C_1-C_8 alkoxy-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^6)_2$, amino C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl-R^7, C_1-C_8 alkyl-NHR^7, carbonitrile, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_8 alkyl, NR^8R^9-C_1-C_8 alkyl, nitro, cyano, O-R^{10}, C_1-C_4 alkyl-OR^{10}, C_1-C_8 alkyl-COR^{11}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7 and R^8 are each independently selected from -H, C_1-C_8 alkyl, C_1-C_4 alkyl-R^{11}, C_1-C_8 alkyl-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, aryl, and arylalkyl, wherein aryl and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^9 and R^{10} are each independently selected from -H, hydroxyl, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{17}, C_1-C_8 alkyl-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_8 alkyl-CO_2R^{16}, C_1-C_8 alkyl-$CONH$-R^{16}, C_1-C_8 alkyl-$CON(R^{16})_2$, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkoxy, halo C_1-C_4 alkyl, $Si(R^{13})_2R^{17}$, aryl, heteroaryl, heterocyclyl, arylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxyl, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, wherein heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, hydroxyl, oxo, C_1-C_8 alkyl, hydroxyl C_1-C_8 alkyl-R^{11}, C_1-C_{10} alkoxy, amino, amino C_1-C_4 alkyl-R^7, NHR^7, $N(R^7)_2$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NHR^8R^9, C_1-C_8 alkyl-$N(R^8)_2$, C_1-C_8 alkyl-R^{11}, C_1-C_8 alkyl-$CO_2R^7R^{11}$, C_1-C_8 alkoxy-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_8 alkyl-SR^{10}, halo, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy,

aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, COR^{33}, and aryl;

R^{15} and R^{16} are each independently selected from -H, aryl, arylalkyl, wherein aryl, arylalkyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{19}, NHR^{19}, aryl, heteroarylalkyl, and heterocyclylalkyl, wherein aryl is optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, hydroxyl, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, amino, amino C_1-C_8 alkyl, $N(R^{19})_2$, C_1-C_8 alkyl-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, heteroaryl, heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are each independently selected from –H and C_1-C_8 alkyl;

R^{23} is selected from –H and C_1-C_8 alkyl;

R^{24} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, CO_2R^{29}, halo, and halo C_1-C_4 alkyl;

R^{29} is selected from -H, and C_1-C_8 alkyl;

R^{30} is selected from -H, aryl, heteroaryl, heterocyclyl, alkylaryl, arylalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{36};

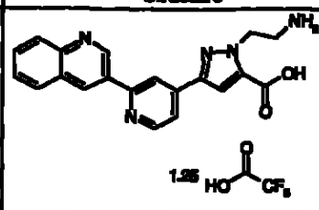
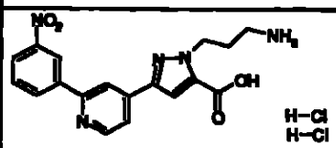
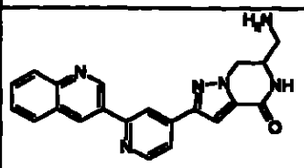
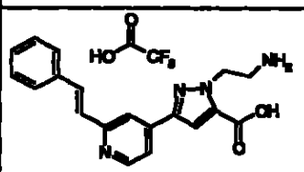
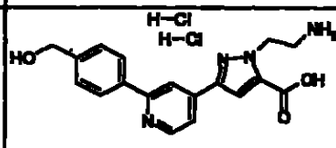
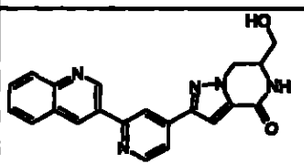
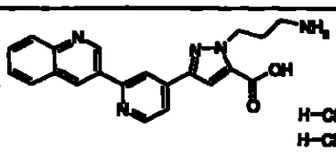
R^{36} is selected from –H and halo;

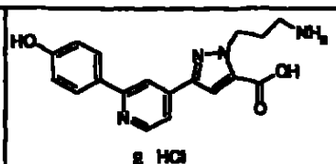
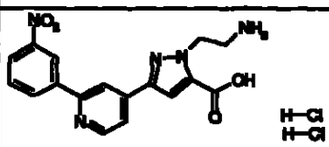
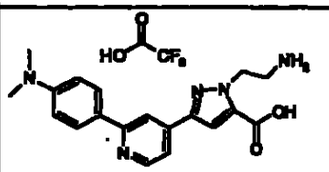
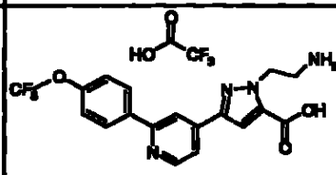
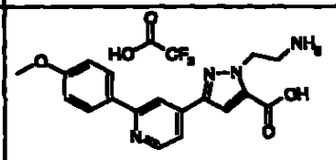
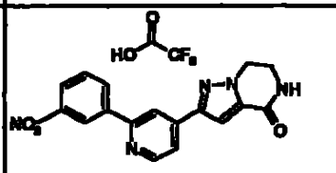
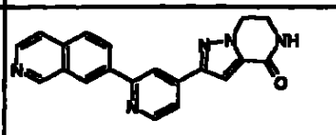
R^2, R^3, R^4, R^{37} and R^{38} are each independently selected from an R^1 group;

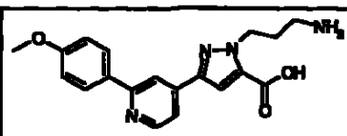
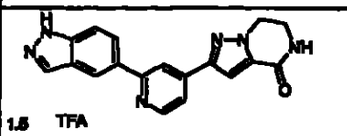
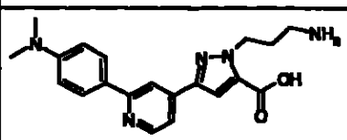
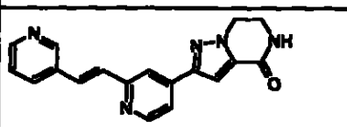
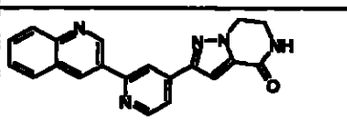
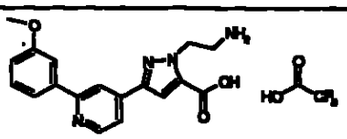
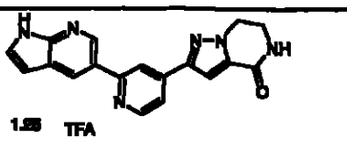
n is 0; and

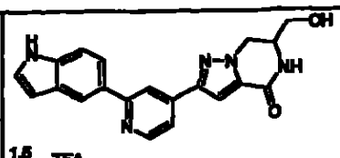
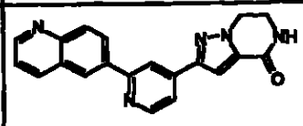
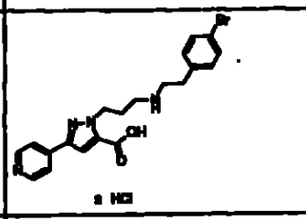
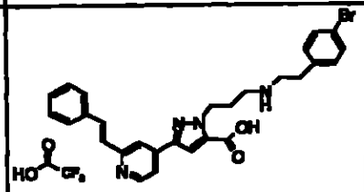
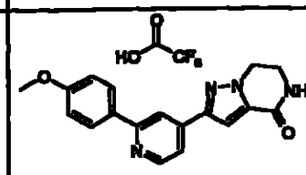
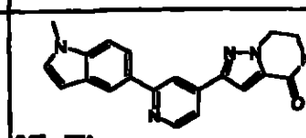
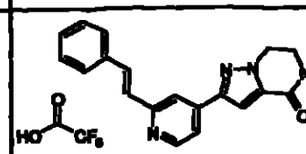
R^3 and R^4 optionally join to form a ring of 5, 6, 7, or 8 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

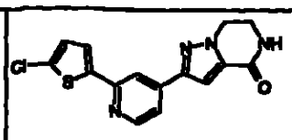
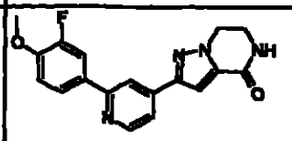
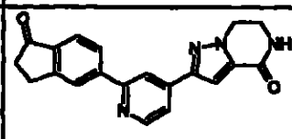
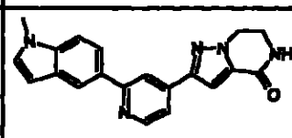
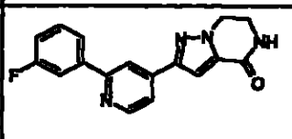
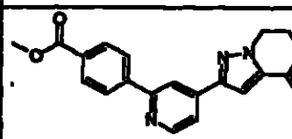
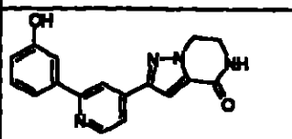
[00038] Table I and Table II show examples of MK-2 inhibiting compounds of the present invention, and also shows the chemical name and, where available, the IC_{50} value of the compound for MK-2 inhibition. It is believed that any of the compounds that are listed in Table I and Table II are MK-2 inhibiting compounds that can be used in the method of the present invention. However, neither the novel MK-2 inhibiting compounds, nor the uses of an MK-2 inhibiting compound that are described herein are intended to be limited to the compounds that are presented in the following Tables.

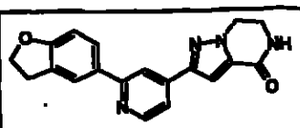
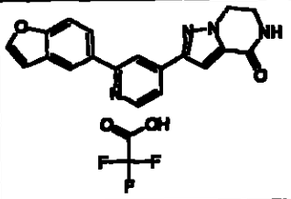
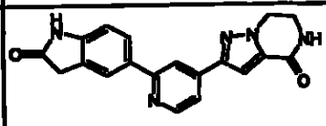
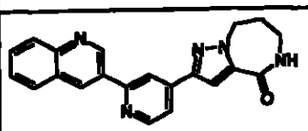
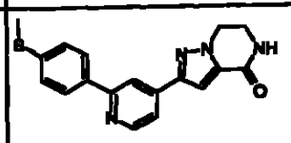
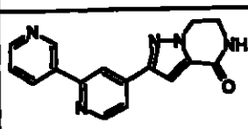
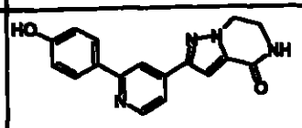
Table I: MK-2 Inhibiting Compounds			
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC_{50} (uM)
1		1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.0288
2		1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride	0.0397
3		6-(aminomethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.0477
4		1-(2-aminoethyl)-3-[2-[(E)-2-phenylethenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.0606
5		1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride	0.0588
6		6-(hydroxymethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.0615
7		1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid dihydrochloride	0.0690

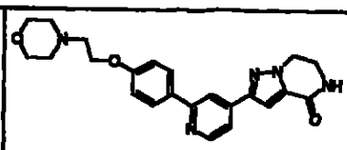
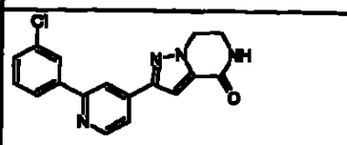
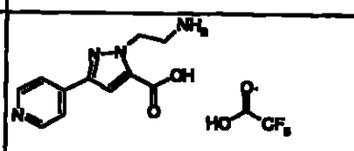
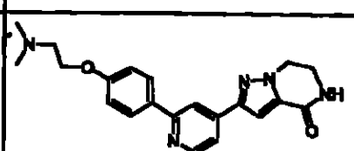
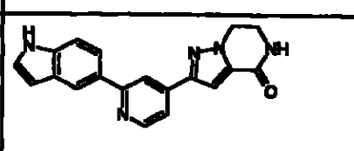
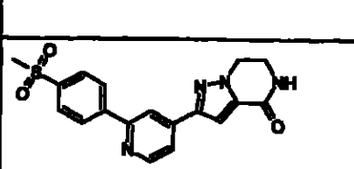
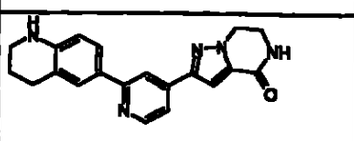
8		1-(3-aminopropyl)-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	0.102
9		1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride	0.108
10		1-(2-aminoethyl)-3-[2-(4-(dimethylamino)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.117
11		1-(2-aminoethyl)-3-[2-(4-(trifluoromethoxy)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.161
12		1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.166
13		2-[2-(3-nitrophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.171
14		2-(2-isoquinolin-7-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.194

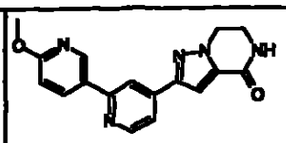
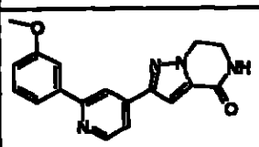
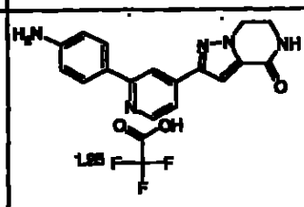
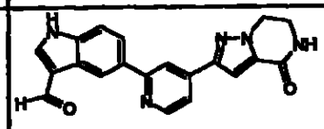
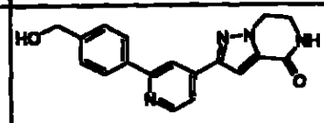
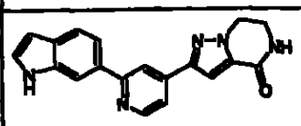
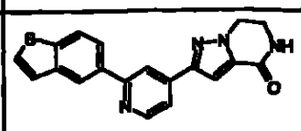
16	 2 HCl	1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	0.166
18	 1.5 TFA	2-[2-(1H-indazol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.189
17	 2 HCl	1-(3-aminopropyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	0.203
18		2-[2-[(E)-2-pyridin-3-ylethenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.212
19		2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.216
20		1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.217
21	 1.55 TFA	2-[2-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.228

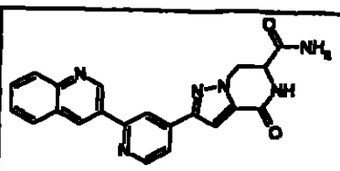
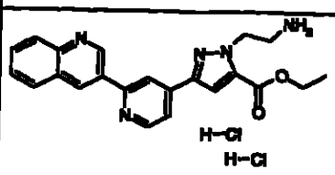
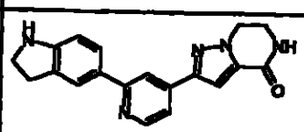
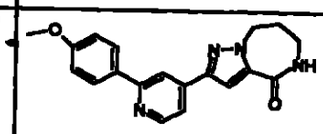
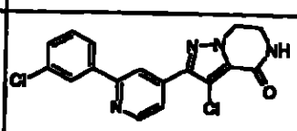
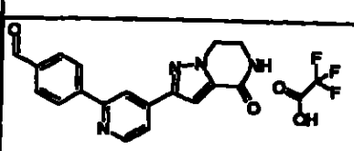
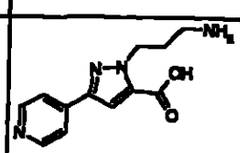
22	 1.5 TFA	6-(hydroxymethyl)-6-[2-(1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.28
23		2-(2-quinolin-6-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.298
24	 2 HCl	1-(3-[[2-(4-bromophenyl)ethyl]amino]propyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid hydrochloride	0.3
25		1-(3-[[2-(4-bromophenyl)ethyl]amino]propyl)-3-[2-[(E)-2-phenylethenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.315
26		2-[2-(4-methoxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.318
27	 2.25 TFA	2-[2-(1-methyl-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.322
28		2-[2-[(E)-2-phenylvinyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.371

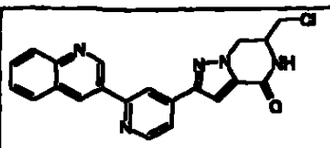
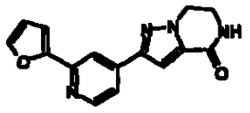
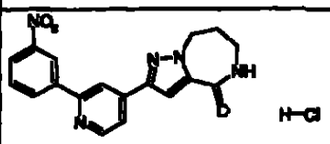
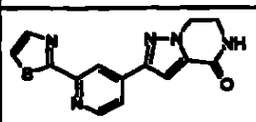
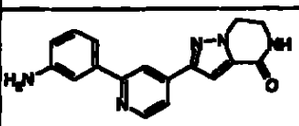
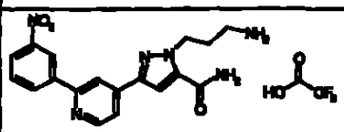
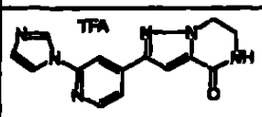
29		2-[2-(5-chlorothien-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.444
30		2-[2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.471
31		2-[2-(1-oxo-2,3-dihydro-1H-inden-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.478
32		2-[2-(1-methyl-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.479
33		2-[2-(3-fluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.503
34		methyl 4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzoate	0.511
35		2-[2-(3-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.52

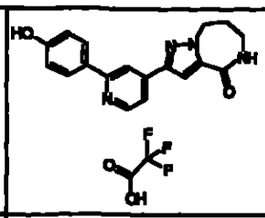
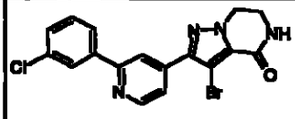
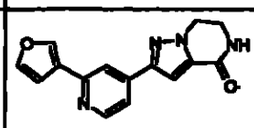
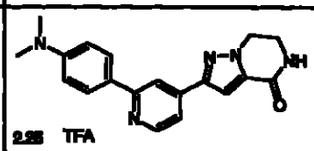
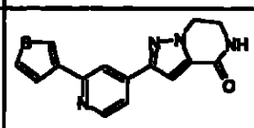
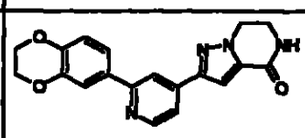
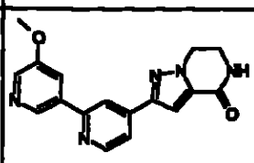
36		2-[2-(2,3-dihydro-1-benzofuran-6-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.521
37		2-[2-(1-benzofuran-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.543
38		2-[2-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.554
39		2-(2-quinolin-3-ylpyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	0.577
40		2-[2-[4-(methylthio)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.581
41		2-(2,3'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.586
42		2-[2-(4-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.611

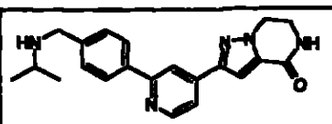
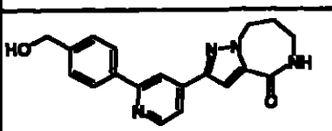
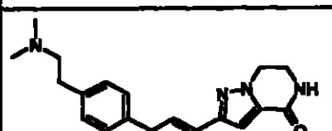
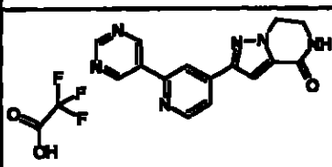
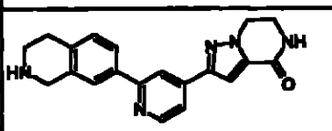
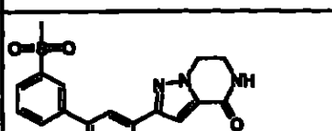
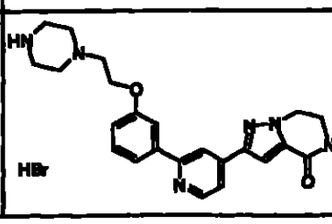
43		2-[2-[4-(2-morpholin-4-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.	0.83
44		2-[2-(3-chlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.836
45		1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.795
46		2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.766
47		2-[2-(1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.808
48		2-[2-[4-(methylsulfonyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.821
49		2-[2-(1,2,3,4-tetrahydroquinolin-6-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.835

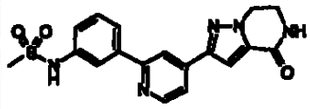
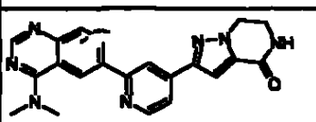
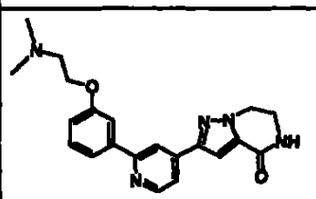
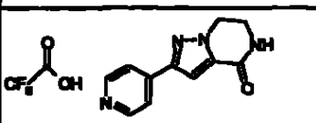
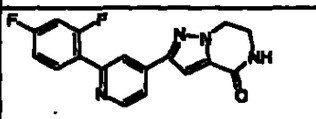
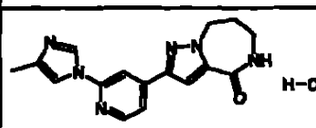
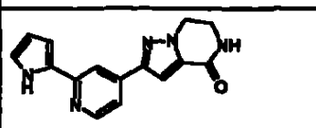
60		2-(6'-methoxy-2,3'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.888
61		2-[2-(3-methoxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.906
62		2-[2-(4-aminophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.914
63		6-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]-1H-indole-3-carbaldehyde	0.922
64		2-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.928
65		2-[2-(1H-indol-6-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.93
66		2-[2-(1-benzothien-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.965

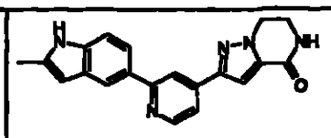
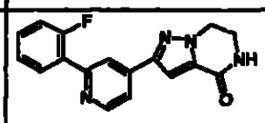
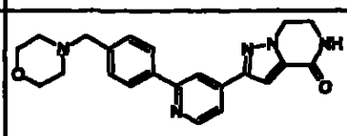
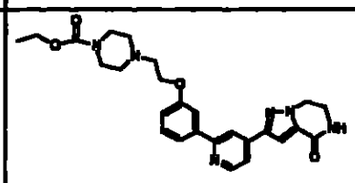
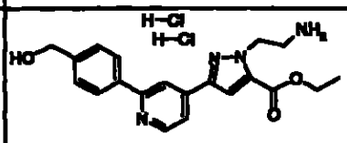
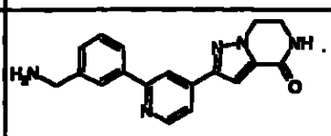
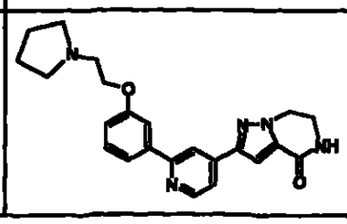
57		4-oxo-2-(2-quinolin-3-ylpyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-6-carboxamide	1.01
58		ethyl 1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride	1.03
59		2-[2-(2,3-dihydro-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.07
60		2-[2-(4-methoxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	1.08
61		3-chloro-2-[2-(3-chlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.13
62		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzaldehyde trifluoroacetate	1.16
63		1-(3-aminopropyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid	1.16

64		15012 or 8-(chloromethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.17
65		2-[2-(2-furyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.2
66		2-[2-(3-nitrophenyl)pyridin-4-yl]-6,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	1.26
67		2-[2-(1,3-thiazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.22
68		2-[2-(3-aminophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.3
69		1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxamide trifluoroacetate	1.22
70		2-[2-(1H-imidazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	1.36

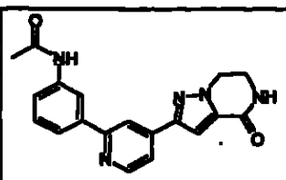
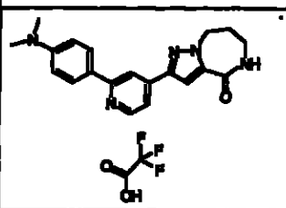
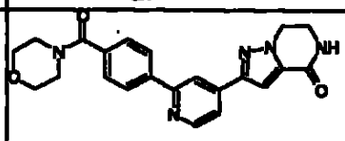
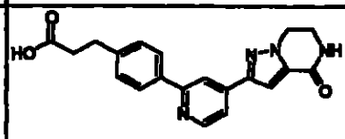
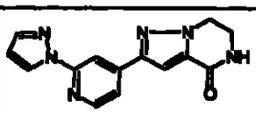
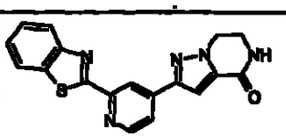
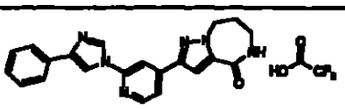
71		2-[2-(4-hydroxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	1.37
72		3-bromo-2-[2-(3-chlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.39
73		2-[2-(3-furyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.46
74	 2.25 TFA	2-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	1.53
75		2-(2-thien-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.55
76		2-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.56
77		2-(5'-methoxy-2,3'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.69

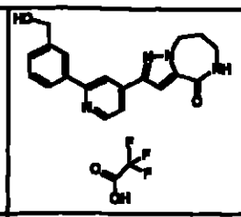
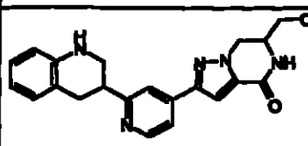
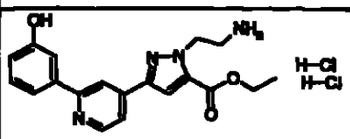
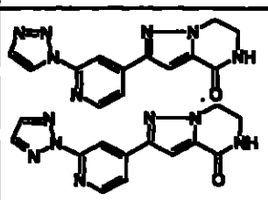
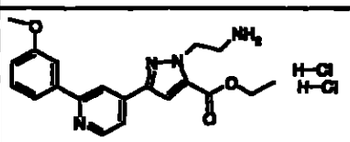
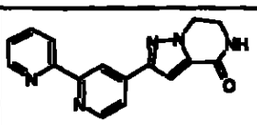
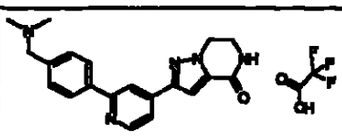
78		2-[2-[4-[(isopropylamino)methyl]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.73
79		2-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	1.76
80		2-[2-[4-[2-(dimethylamino)ethyl]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.99
81		2-(2-pyrimidin-5-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	1.99
82		2-[2-(1,2,3,4-tetrahydroisoquinolin-7-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.09
83		2-[2-[3-(methylsulfonyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.1
84		2-[2-[3-(2-piperazin-1-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrobromide	2.13

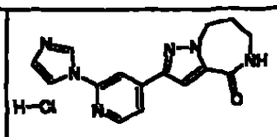
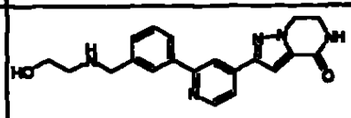
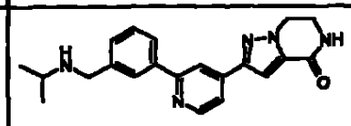
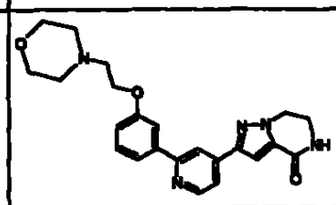
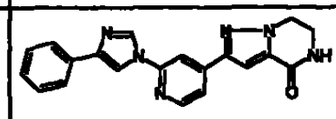
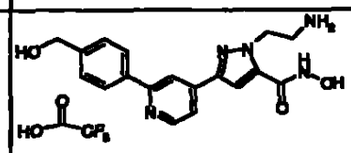
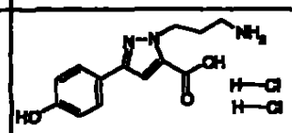
86		N-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]methanesulfonamide	2.29
86		2-[2-[4-(dimethylamino)quinazolin-6-yl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.4
87		2-[2-[3-[2-(dimethylamino)ethoxy]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.4
88		2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	2.8
89		2-[2-(2,4-difluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.82
90		2-[2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	2.76
91		2-[2-(1H-pyrrol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.79

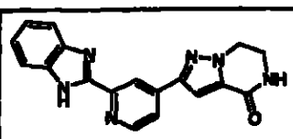
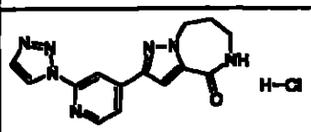
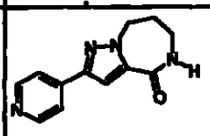
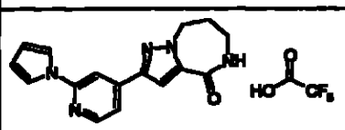
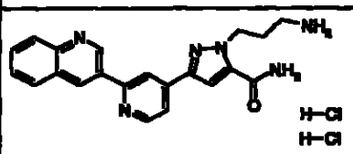
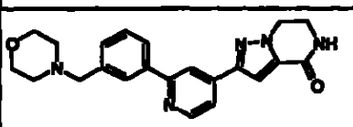
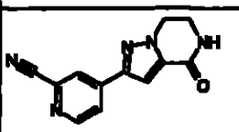
92		2-[2-(2-methyl-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.83
93		2-[2-(2-fluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.95
94		2-[2-[4-(morpholin-4-ylmethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.99
95		ethyl 4-(2-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenoxy]ethyl)piperazine-1-carboxylate	3.02
96		ethyl 1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	3.25
97		2-[2-[3-(aminomethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	3.25
98		2-[2-[3-(2-pyrrolidin-1-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	3.27

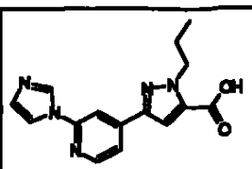
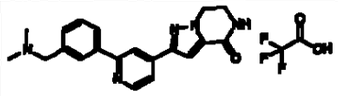
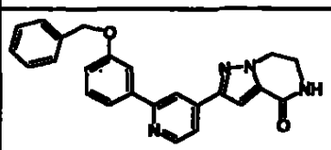
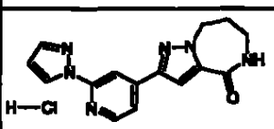
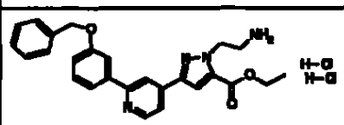
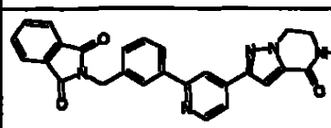
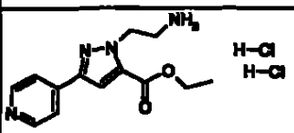
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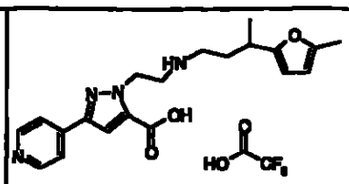
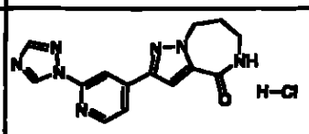
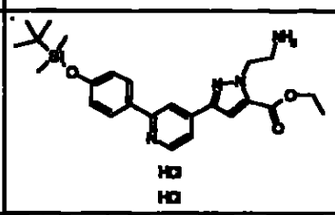
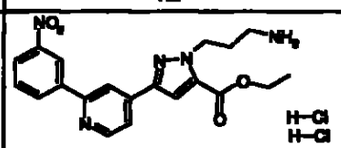
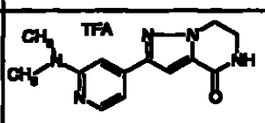
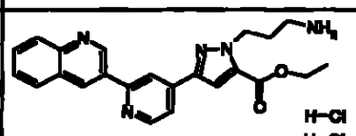
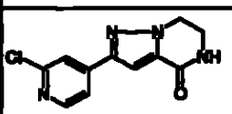
99		N-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]acetamide	3.31
100		2-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	3.44
101		2-[2-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	3.65
102		3-[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]propanoic acid	4.19
103		2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.2
104		2-[2-(1,3-benzothiazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.27
105		2-[2-(4-phenyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	4.31

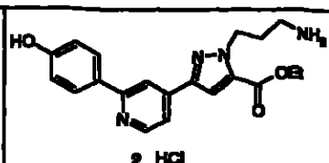
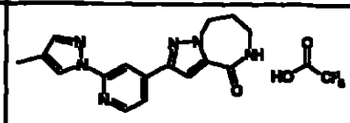
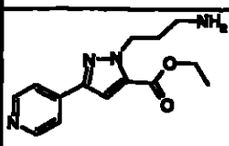
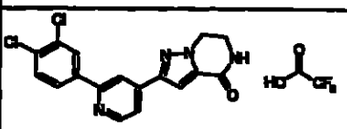
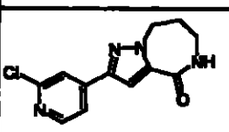
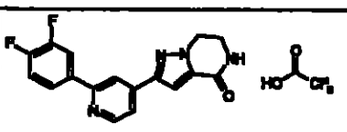
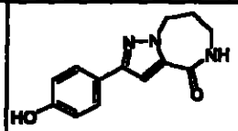
106		2-[2-[3-(hydroxymethyl)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	4.54
107		6-(hydroxymethyl)-2-[2-(1,2,3,4-tetrahydroquinolin-3-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.9
108		ethyl 1-(2-aminoethyl)-3-[2-(3-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	4.98
109		2-[2-(2H-1,2,3-triazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one compound with 2-[2-(1H-1,2,3-triazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (1:1)	5.21
110		ethyl 1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	5.23
111		2-(2,2'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	5.34
112		2-(2-[4-[(dimethylamino)methyl]phenyl]pyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	5.35

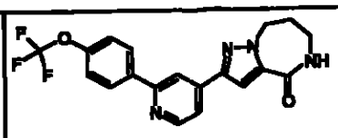
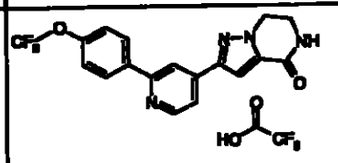
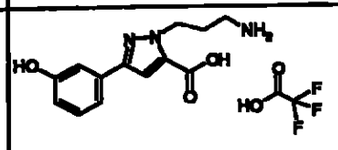
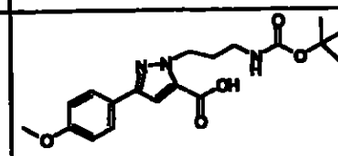
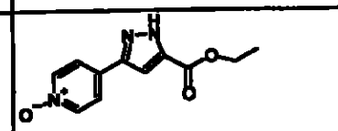
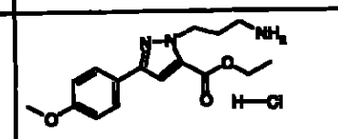
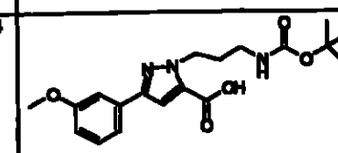
113		2-[2-(1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	6.66
114		2-[2-(3-[(2-hydroxyethyl)amino]methyl}phenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	6.76
115		2-{2-[3-[(isopropylamino)methyl]phenyl}pyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	6.27
116		2-{2-[3-(2-morpholin-4-ylethoxy)phenyl]pyridin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	6.73
117		2-[2-(4-phenyl-1H-imidazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	7.04
118		1-(2-aminoethyl)-N-hydroxy-3-[2-{4-(hydroxymethyl)phenyl}pyridin-4-yl)-1H-pyrazole-5-carboxamide trifluoroacetate	7.91
119		1-(3-aminopropyl)-3-(4-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid dihydrochloride	8.11

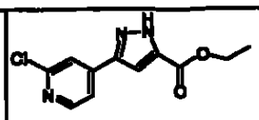
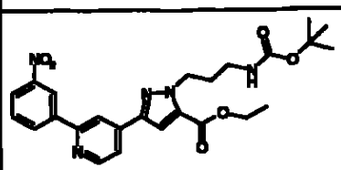
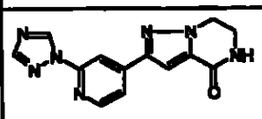
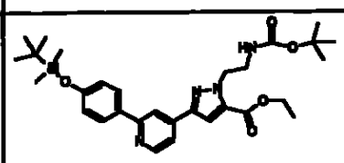
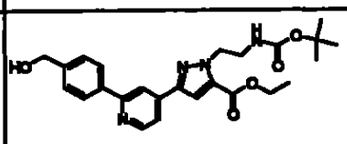
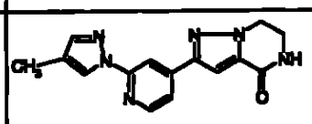
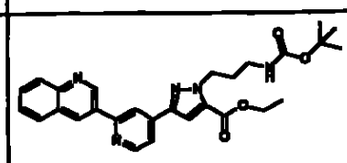
120		2-[2-(1H-benzimidazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	8.02
121		2-[2-(1H-1,2,3-triazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	9.05
122		2-pyridin-4-yl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	10.1
123		2-[2-(1H-pyrrol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	10.6
124		1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxamide dihydrochloride	10.7
125		2-[2-[3-(morpholin-4-ylmethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	11.4
126		4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridine-2-carbonitrile	13.8

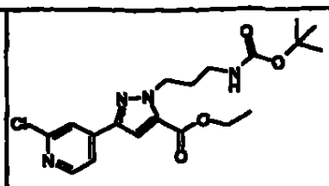
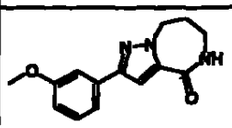
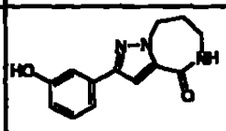
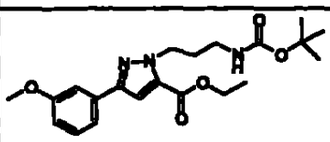
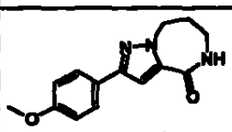
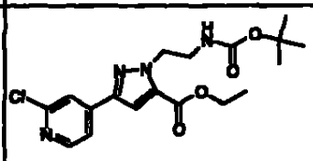
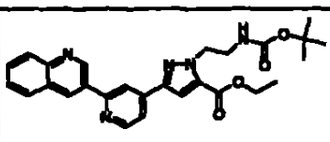
127		3-[2-(1H-imidazol-1-yl)pyridin-4-yl]-1-propyl-1H-pyrazole-5-carboxylic acid	14.3
128		2-[2-[3-[(dimethylamino)methyl]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	15.4
129		2-[2-[3-(benzyloxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	15.5
130		2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	16.2
131		ethyl 1-(2-aminoethyl)-3-[2-[3-(benzyloxy)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	20
132		2-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzyl]-1H-isoindole-1,3(2H)-dione	20
133		ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride	24.8

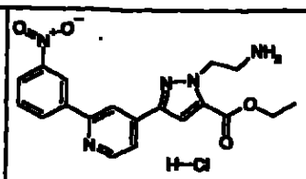
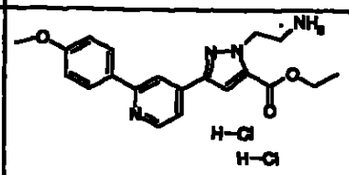
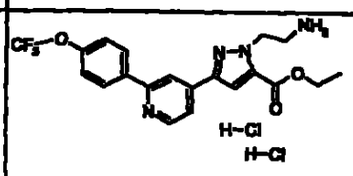
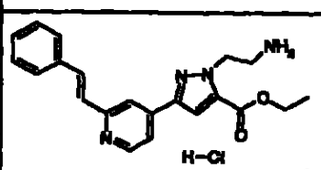
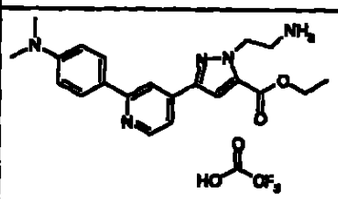
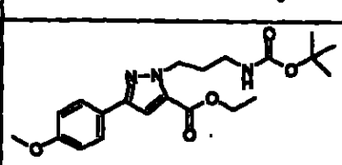
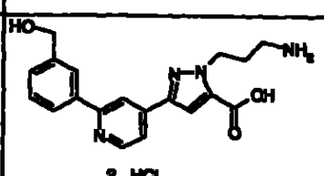
134		1-[2-[[3-(5-methyl-2-furyl)butyl]amino]ethyl]-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate	27.2
135		2-[2-(1H-1,2,4-triazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	28.2
136		ethyl 1-(2-aminoethyl)-3-[2-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	29.3
137		ethyl 1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	31.6
138		2-[2-(dimethylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	37.2
139		ethyl 1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride	38.6
140		2-(2-chloropyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	44.8

141	 2 HCl	ethyl 1-(3-aminopropyl)-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride	47.5
142		2-[2-(4-methyl-1H-pyrazol-1-yl)pyridin-4-yl]-6,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	58.4
143	 HCl	ethyl 1-(3-aminopropyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate hydrochloride	60.6
144		2-[2-(3,4-dichlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	65.5
145		2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	80.4
146		2-[2-(3,4-difluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	68.9
147		2-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	118

148		2-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	124
149		2-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	131
150		1-(3-aminopropyl)-3-(3-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid trifluoroacetate	153
151		1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid	155
152		ethyl 3-(1-oxidopyridin-4-yl)-1H-pyrazole-5-carboxylate	200
153		ethyl 1-(3-aminopropyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate hydrochloride	200
154		1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylic acid	200

155		ethyl 3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate	200
156		ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate	200
157		2-[2-(1H-1,2,4-triazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	200
158		ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-[2-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate	200
159		ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate	200
160		2-[2-(4-methyl-1H-pyrazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	200
161		2-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	200

162		ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate	200
163		2-(3-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	200
164		2-(3-hydroxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	200
165		ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylate	200
166		2-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	200
167		ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate	
168		ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate	

169		ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
170		ethyl 1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
171		ethyl 1-(2-aminoethyl)-3-[2-(4-(trifluoromethoxy)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
172		ethyl 1-(2-aminoethyl)-3-[2-((E)-2-phenylethenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
173		ethyl 1-(2-aminoethyl)-3-[2-(4-(dimethylamino)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate trifluoroacetate	
174		ethyl 1-(3-[(tert-butoxycarbonyl)amino]propyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate	
175		1-(3-aminopropyl)-3-(2-[3-(hydroxymethyl)phenyl]pyridin-4-yl)-1H-pyrazole-5-carboxylic acid hydrochloride	

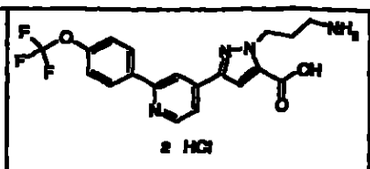
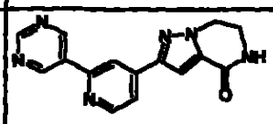
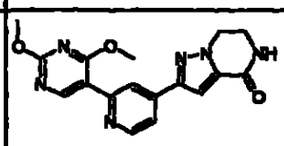
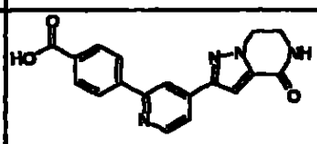
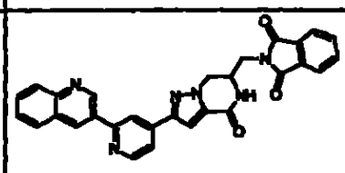
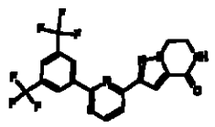
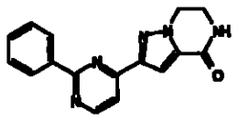
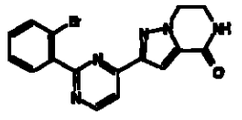
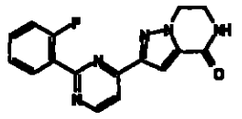
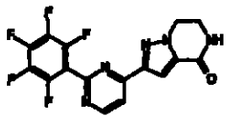
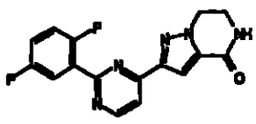
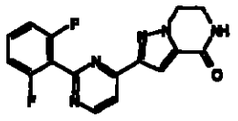
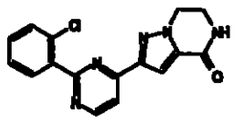
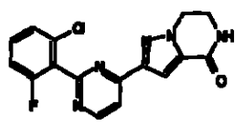
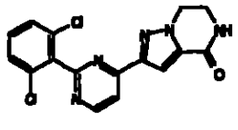
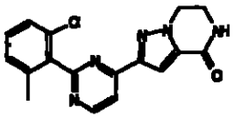
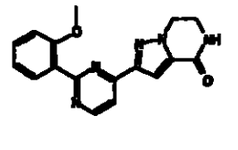
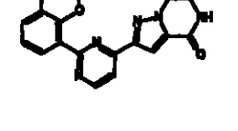
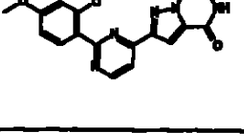
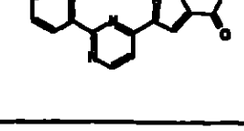
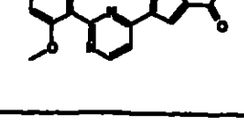
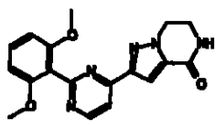
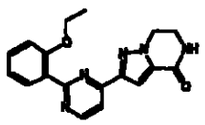
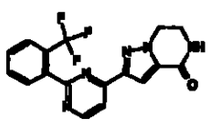
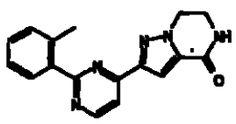
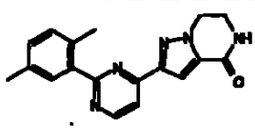
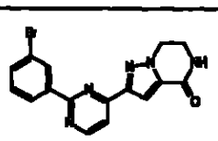
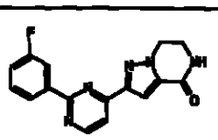
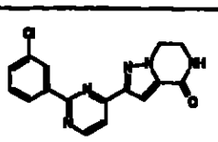
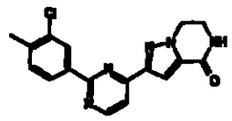
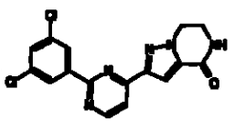
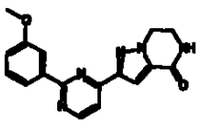
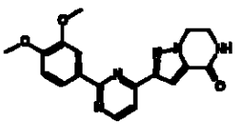
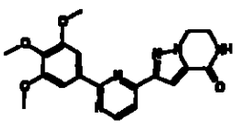
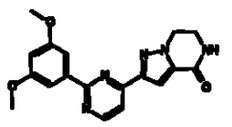
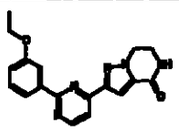
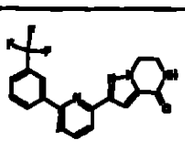
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177		2-(2-pyrimidin-5-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
178		2-[2-(2,4-dimethoxypyrimidin-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
179		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzoic acid	
180		2-[[4-oxo-2-(2-quinolin-3-ylpyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-5-yl]methyl]-1H-isoindole-1,3(2H)-dione	

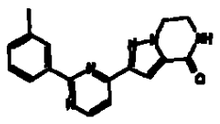
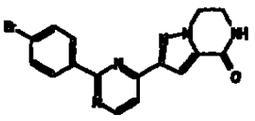
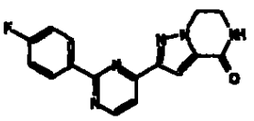
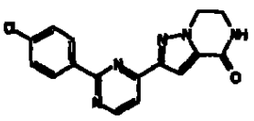
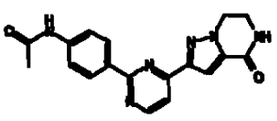
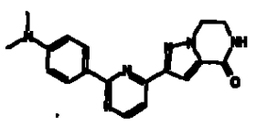
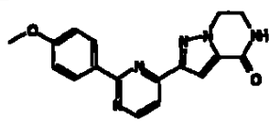
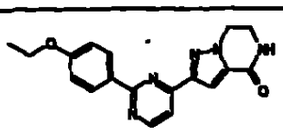
Table II: Additional MK-2 Inhibiting Compounds			
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC_{50} (uM)
181		2-[2-[3,5-bis(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
182		2-(2-phenylpyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
183		2-[2-(2-bromophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
184		2-[2-(2-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
185		2-[2-(pentafluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
186		2-[2-(2,5-difluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
187		2-[2-(2,6-difluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
188		2-[2-(2-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

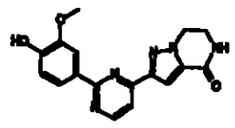
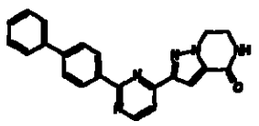
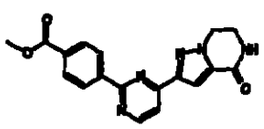
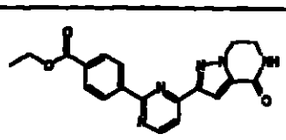
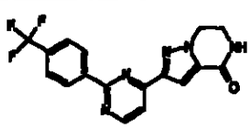
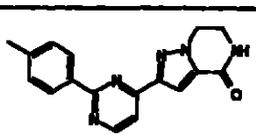
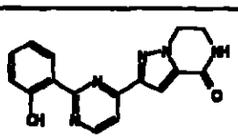
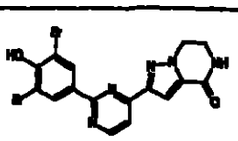
189		2-[2-(2-chloro-6-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
190		2-[2-(2,6-dichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
191		2-[2-(2-chloro-6-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
192		2-[2-(2-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
193		2-[2-(2,3-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
194		2-[2-(2,3,4-trimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
195		2-[2-(2,4-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
196		2-[2-(2,4,6-trimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

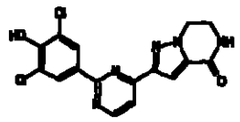
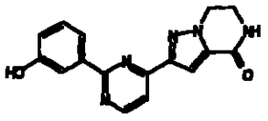
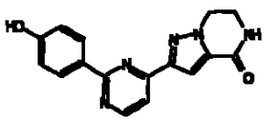
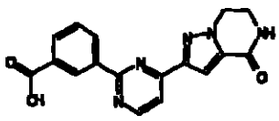
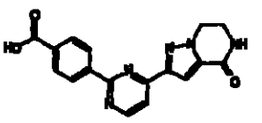
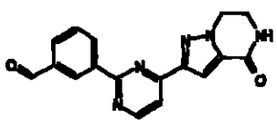
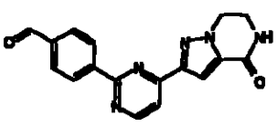
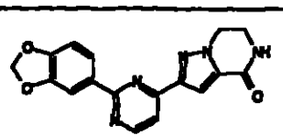
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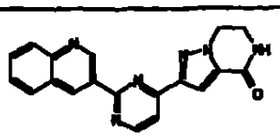
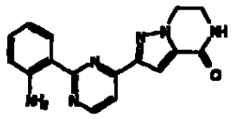
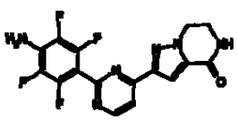
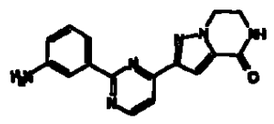
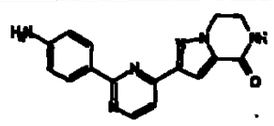
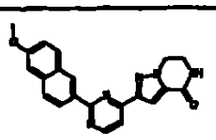
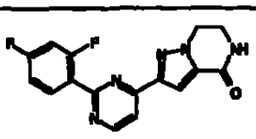
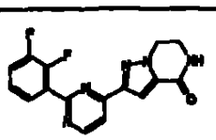
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198		2-[2-(2-ethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
199		2-[2-[2-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
200		2-[2-(2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
201		2-[2-(2,5-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
202		2-[2-(3-bromophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
203		2-[2-(3-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
204		2-[2-(3-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

205		2-[2-(3-chloro-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
206		2-[2-(3,5-dichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
207		2-[2-(3-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
208		2-[2-(3,4-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
209		2-[2-(3,4,5-trimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
210		2-[2-(3,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
211		2-[2-(3-ethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
212		2-[2-(3-(trifluoromethyl)phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

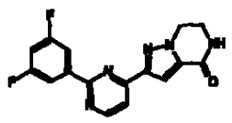
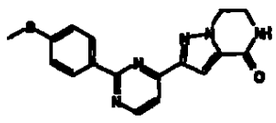
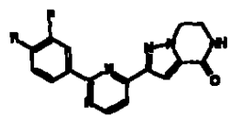
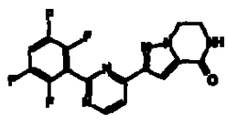
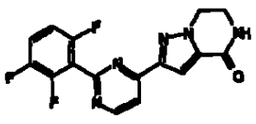
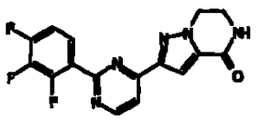
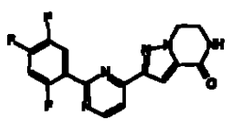
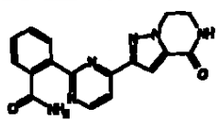
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214		2-[2-(4-bromophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
215		2-[2-(4-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
216		2-[2-(4-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
217		N-(4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl)acetamide	
218		2-[2-[4-(dimethylamino)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
219		2-[2-(4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
220		2-[2-(4-ethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

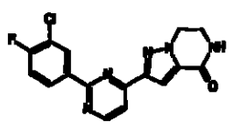
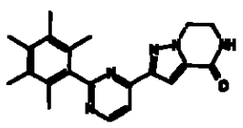
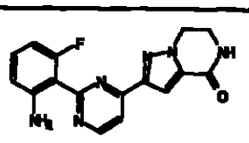
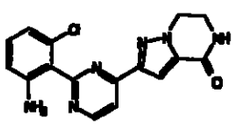
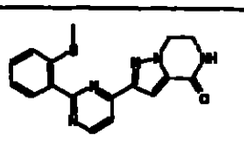
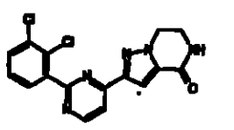
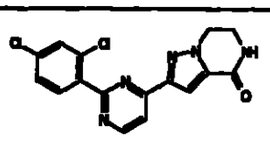
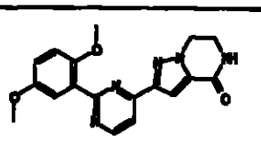
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222		2-[2-(1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
223		methyl 4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoate	
224		ethyl 4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoate	
225		2-[2-[4-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
226		2-[2-(4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
227		2-[2-(2-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
228		2-[2-(3,5-dibromo-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

229		2-[2-(3,5-dichloro-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
230		2-[2-(3-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
231		2-[2-(4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
232		3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
233		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
234		3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzaldehyde	
235		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzaldehyde	
236		2-[2-(1,3-benzodioxol-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

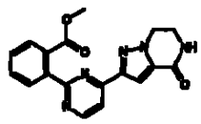
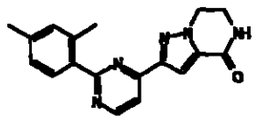
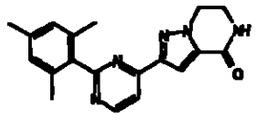
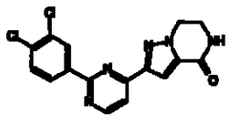
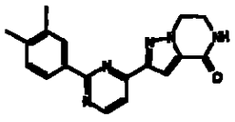
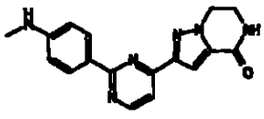
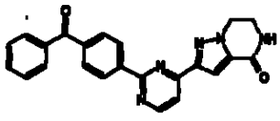
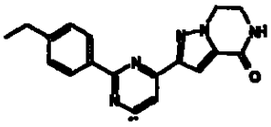
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238		2-[2-(2-aminophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
239		2-[2-(4-amino-2,3,5,6-tetrafluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
240		2-[2-(3-aminophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
241		2-[2-(4-aminophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
242		2-[2-(6-methoxy-2-naphthyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
243		2-[2-(2,4-difluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
244		2-[2-(2,3-difluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

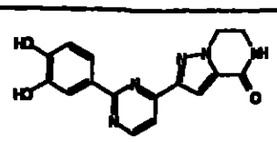
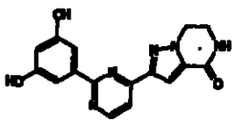
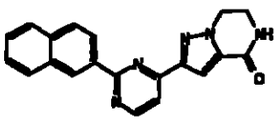
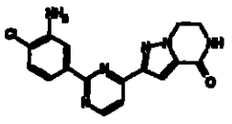
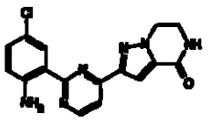
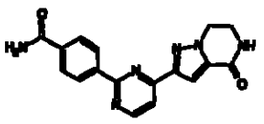
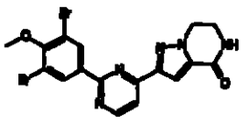
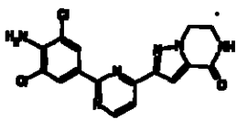
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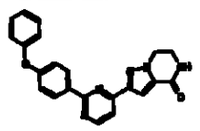
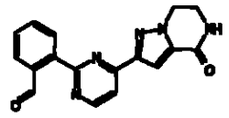
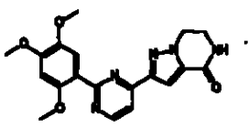
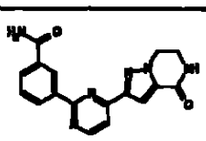
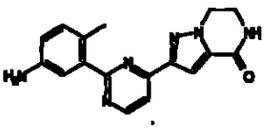
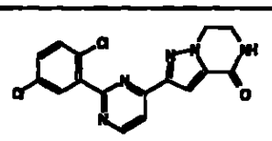
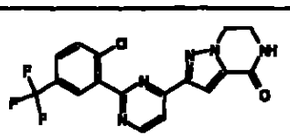
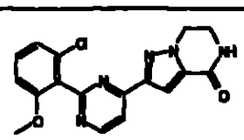
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246		2-[2-[4-(methylthio)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
247		2-[2-(3,4-difluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
248		2-[2-(2,3,5,6-tetrafluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
249		2-[2-(2,3,6-trifluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
250		2-[2-(2,3,4-trifluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
251		2-[2-(2,4,5-trifluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
252		2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzamide	

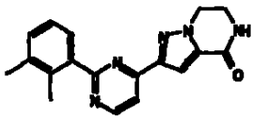
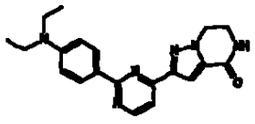
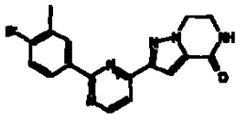
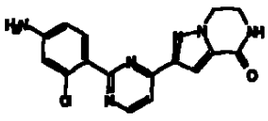
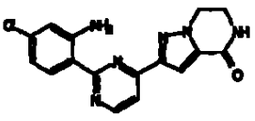
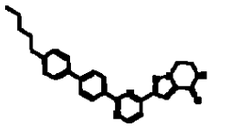
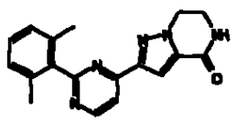
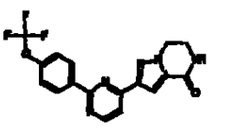
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257		2-[2-[2-(methylthio)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
258		2-[2-(2,3-dichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
259		2-[2-(2,4-dichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
260		2-[2-(2,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

46 45

281		methyl 2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoate	
282		2-[2-(2,4-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
283		2-(2-methylpyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
284		2-[2-(3,4-dichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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287		2-[2-(4-benzoylphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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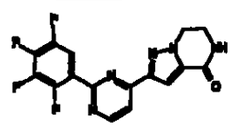
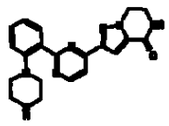
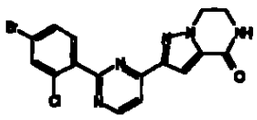
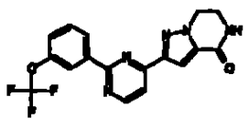
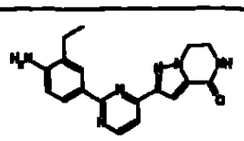
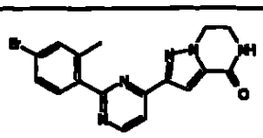
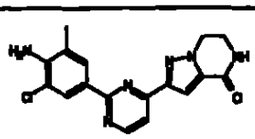
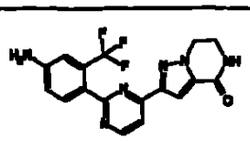
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271		2-[2-(2-naphthyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
272		2-[2-(3-amino-4-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
273		2-[2-(2-amino-5-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
274		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzamide	
275		2-[2-(3,5-dibromo-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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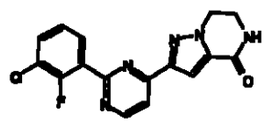
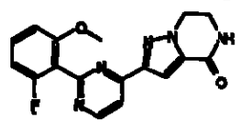
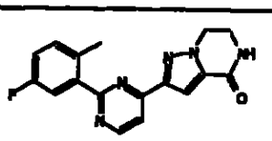
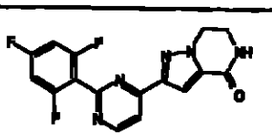
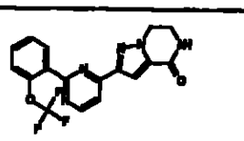
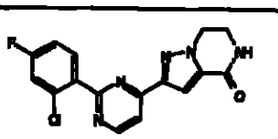
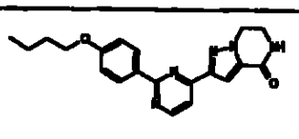
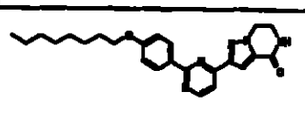
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278		2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzaldehyde	
279		2-[2-(2,4,5-trimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
280		3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzamide	
281		2-[2-(5-amino-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
282		2-[2-(2,5-dichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
283		2-[2-[2-chloro-5-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
284		2-[2-(2-chloro-6-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

285		2-[2-(2,3-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
286		2-[2-[4-(diethylamino)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
287		2-[2-(4-bromo-3-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
288		2-[2-(4-amino-2-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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291		2-[2-(2,6-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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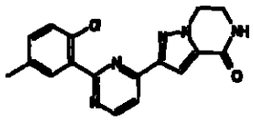
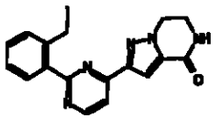
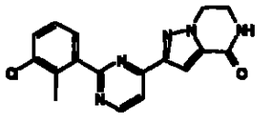
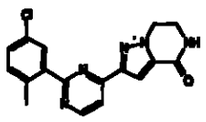
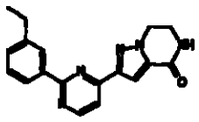
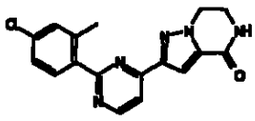
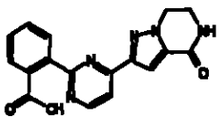
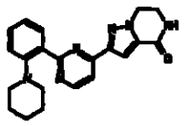
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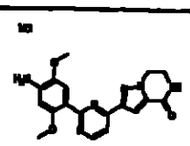
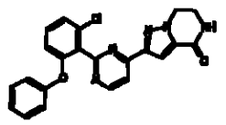
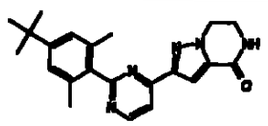
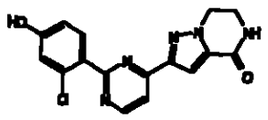
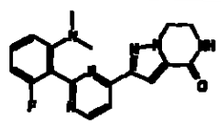
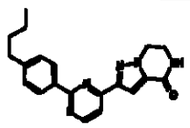
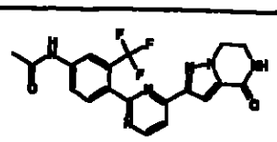
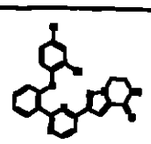
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294		2-[2-(2-piperazin-1-ylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
295		2-[2-(4-bromo-2-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
296		2-[2-[3-(trifluoromethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
297		2-[2-(4-amino-3-ethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
298		2-[2-(4-bromo-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
299		2-[2-(4-amino-3-chloro-5-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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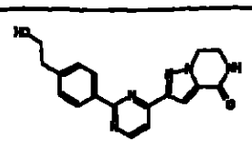
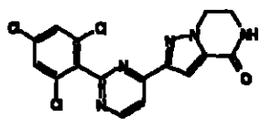
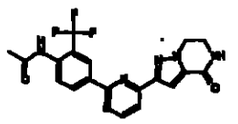
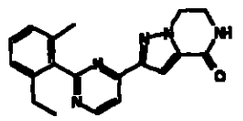
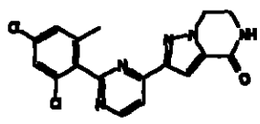
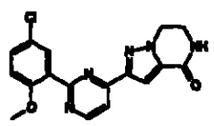
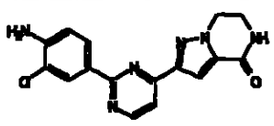
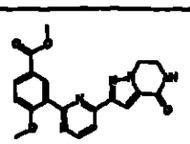
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303		2-[2-(5-fluoro-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
304		2-[2-(2,4,6-trifluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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306		2-[2-(2-chloro-4-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
307		2-[2-(4-butoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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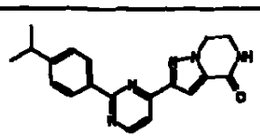
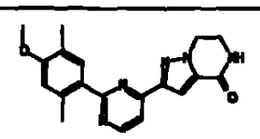
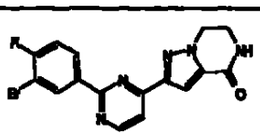
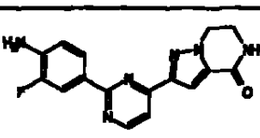
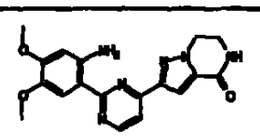
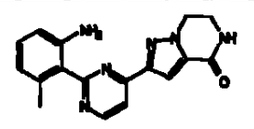
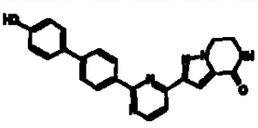
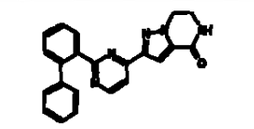
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309		2-[2-(2-chloro-5-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
310		2-[2-(2-ethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
311		2-[2-(3-chloro-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
312		2-[2-(5-chloro-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
313		2-[2-(3-ethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
314		2-[2-(4-chloro-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
315		2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
316		2-[2-(2-piperidin-1-ylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

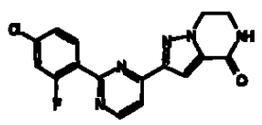
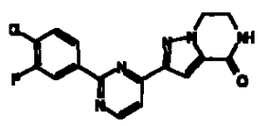
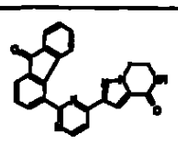
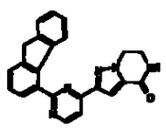
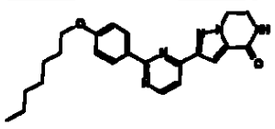
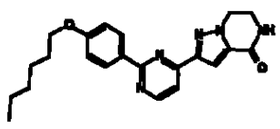
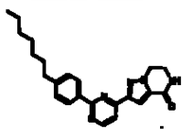
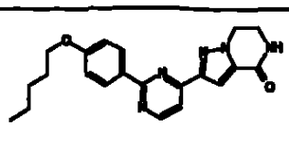
317		2-[2-(4-amino-2,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride	
318		2-[2-(2-chloro-6-phenoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
319		2-[2-(4-tert-butyl-2,6-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
320		2-[2-(2-chloro-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
321		2-[2-[2-(dimethylamino)-6-fluorophenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
322		2-[2-(4-butylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
323		N-[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-3-(trifluoromethyl)phenyl]acetamide	
324		2-[2-[2-(2,4-dichlorophenoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

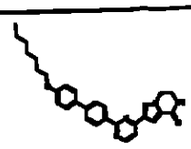
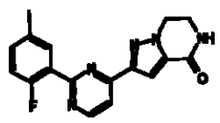
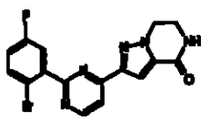
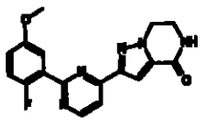
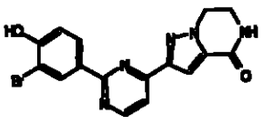
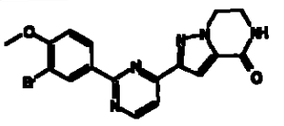
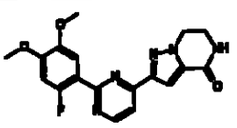
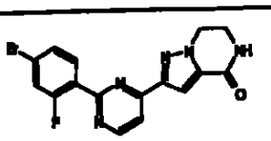
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328		2-[2-(2,4,6-trichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
327		N-[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-2-(trifluoromethyl)phenyl]acetamide	
329		2-[2-(2-ethyl-6-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
329		2-[2-(2,4-dichloro-6-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
330		2-[2-(5-chloro-2-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
331		2-[2-(4-amino-3-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
332		methyl 4-methoxy-3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoate	

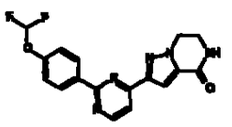
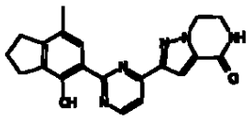
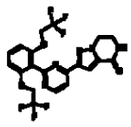
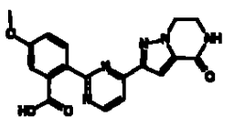
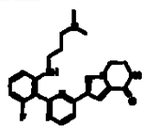
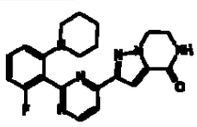
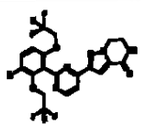
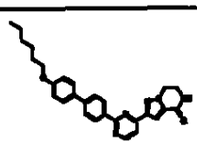
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334		2-[2-(4-methoxy-2,5-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
335		2-[2-(3-bromo-4-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
336		2-[2-(4-amino-3-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
337		2-[2-(2-amino-4,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
338		2-[2-(2-amino-6-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
339		2-[2-(4'-hydroxy-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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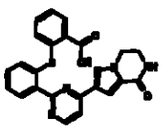
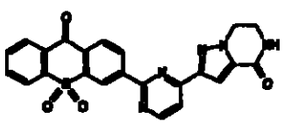
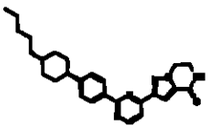
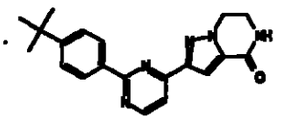
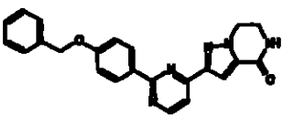
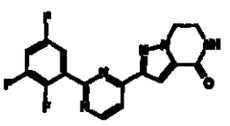
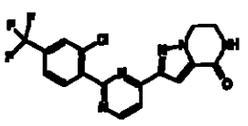
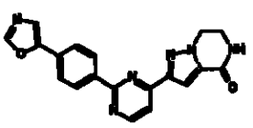
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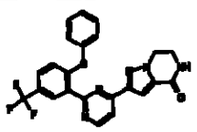
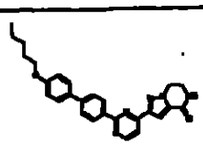
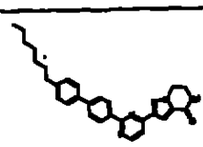
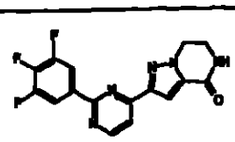
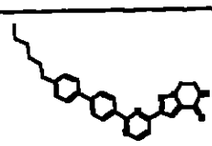
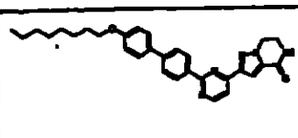
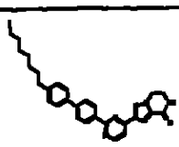
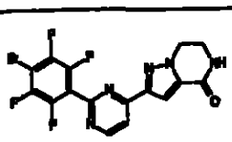
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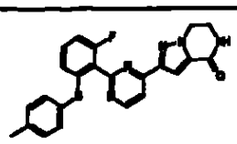
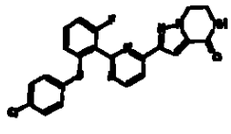
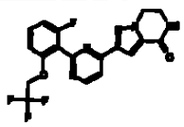
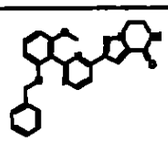
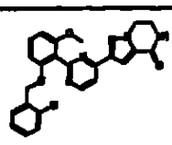
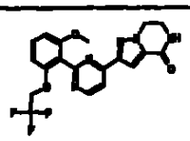
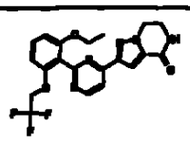
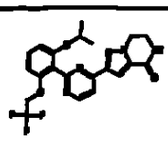
397		2-[2-(4-chloro-2-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
398		2-[2-(4-chloro-3-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
399		2-[2-(9-oxo-9H-fluoren-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
400		2-[2-(9H-fluoren-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
401		2-[2-(4-(heptyloxy)phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
402		2-[2-(4-(hexyloxy)phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
403		2-[2-(4-heptylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
404		2-[2-(4-(pentyloxy)phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

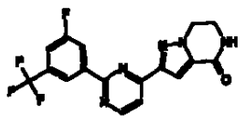
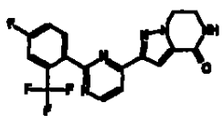
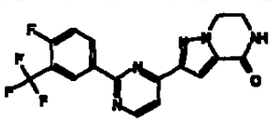
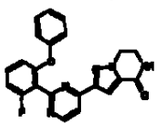
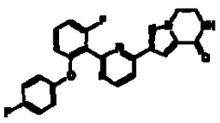
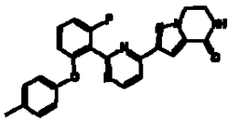
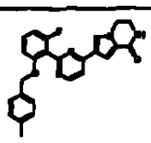
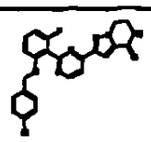
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390		2-[2-(2-fluoro-5-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
391		2-[2-(2-bromo-5-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
392		2-[2-(2-fluoro-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
393		2-[2-(3-bromo-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
394		2-[2-(3-bromo-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
395		2-[2-(2-fluoro-4,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
396		2-[2-(4-bromo-2-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

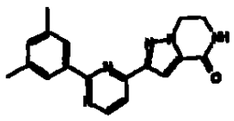
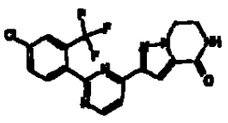
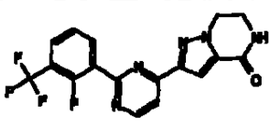
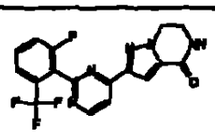
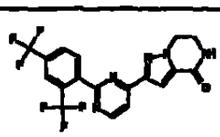
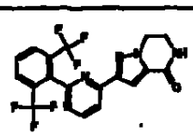
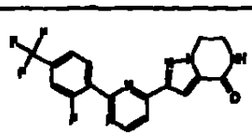
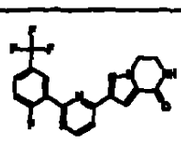
381		2-[2-[4-(difluoromethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
382		2-[2-(4-hydroxy-7-methyl-2,3-dihydro-1H-inden-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
383		2-[2-[2,6-bis(2,2,2-trifluoroethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
384		5-methoxy-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
385		2-[2-[2-[[3-(dimethylamino)propyl]amino]-5-fluorophenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
386		2-[2-(2-fluoro-6-piperidin-1-ylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
387		2-[2-[3-bromo-2,6-bis(2,2,2-trifluoroethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
388		2-[2-[4'-(hexyloxy)-1,1'-biphenyl-4-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

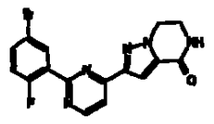
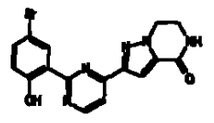
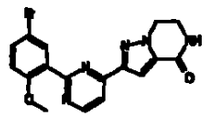
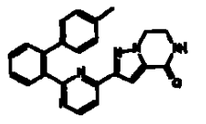
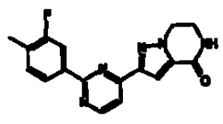
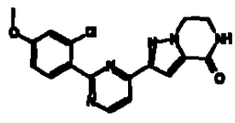
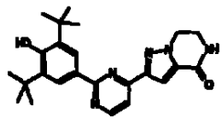
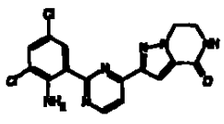
373		2-({3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl}thio)benzoic acid	
374		2-[2-(10,10-dioxido-9-oxo-9H-thioxanthen-3-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
376		2-[2-[4-(4-pentylcyclohexyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
378		2-[2-(4-tert-butylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
377		2-[2-[4-(benzyloxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
379		2-[2-(2,3,5-trifluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
370		2-[2-[2-chloro-4-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
380		2-[2-[4-(1,3-oxazol-5-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

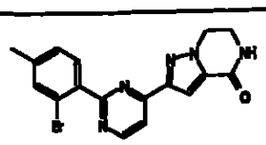
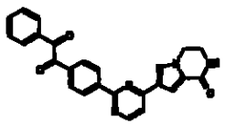
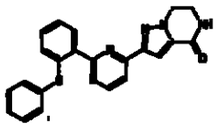
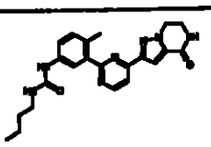
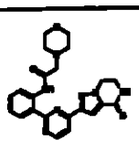
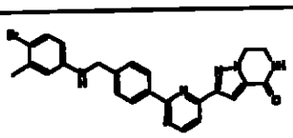
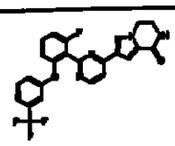
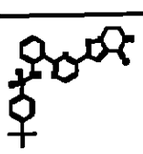
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366		2-[2-(4'-(pentyloxy)-1,1'-biphenyl-4-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
367		2-[2-(4'-heptyl-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
368		2-[2-(3,4,5-trifluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
369		2-[2-(4'-hexyl-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
370		2-[2-(4'-(octyloxy)-1,1'-biphenyl-4-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
371		2-[2-(4'-octyl-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
372		2-[2-(4-bromo-2,3,5,6-tetrafluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

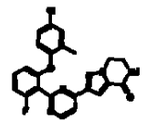
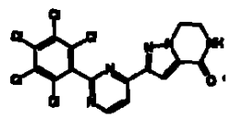
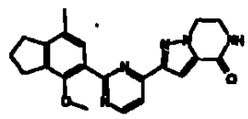
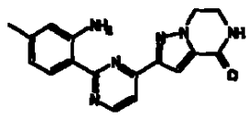
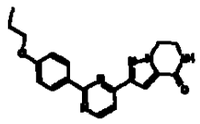
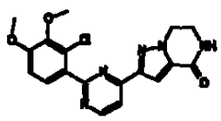
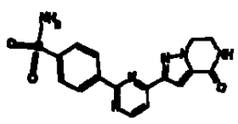
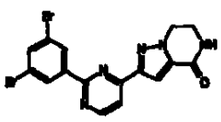
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358		2-{2-[2-[(4-chlorophenyl)thio]-6-fluorophenyl]pyrimidin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
359		2-{2-[2-fluoro-6-(2,2,2-trifluoroethoxy)phenyl]pyrimidin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
360		2-{2-[2-(benzyloxy)-6-methoxyphenyl]pyrimidin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
361		2-{2-[2-[(2-chlorobenzyl)oxy]-6-methoxyphenyl]pyrimidin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
362		2-{2-[2-methoxy-6-(2,2,2-trifluoroethoxy)phenyl]pyrimidin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
363		2-{2-[2-ethoxy-6-(2,2,2-trifluoroethoxy)phenyl]pyrimidin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
364		2-{2-[2-isopropoxy-6-(2,2,2-trifluoroethoxy)phenyl]pyrimidin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

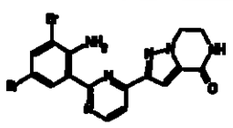
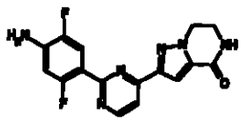
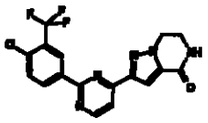
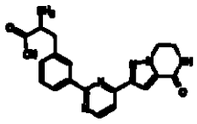
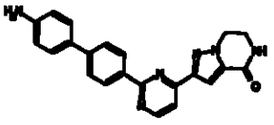
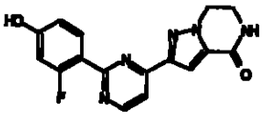
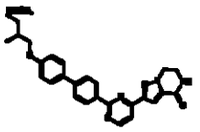
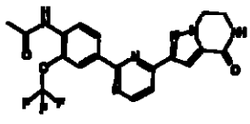
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350		2-[2-[4-fluoro-2-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
351		2-[2-[4-fluoro-3-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
352		2-[2-(2-fluoro-6-phenoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
353		2-[2-[2-fluoro-6-(4-fluorophenoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
354		2-[2-[2-fluoro-6-(4-methylphenoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
355		2-[2-[2-fluoro-6-[(4-methylbenzyl)oxy]phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
356		2-[2-[2-[(4-chlorobenzyl)oxy]-6-fluorophenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

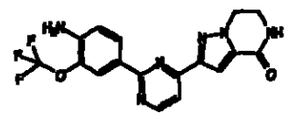
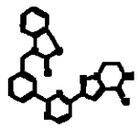
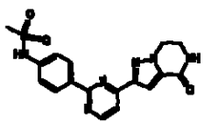
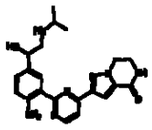
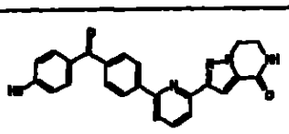
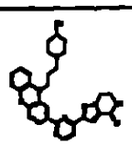
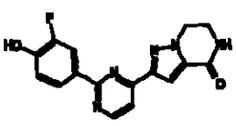
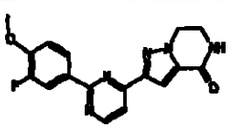
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342		2-[2-[4-chloro-2-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
343		2-[2-[2-fluoro-3-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
344		2-[2-[2-fluoro-6-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
345		2-[2-[2,4-bis(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
346		2-[2-[2,6-bis(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
347		2-[2-[2-fluoro-4-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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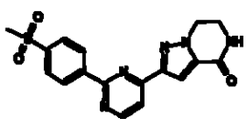
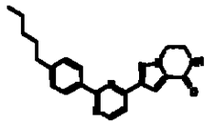
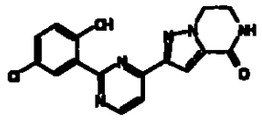
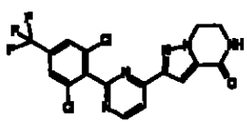
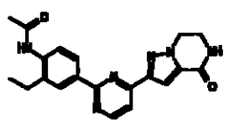
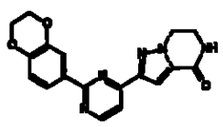
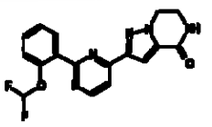
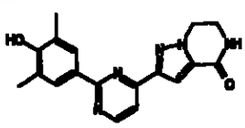
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406		2-[2-(5-bromo-2-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
407		2-[2-(5-bromo-2-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
408		2-[2-(4'-methyl-1,1'-biphenyl-2-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
409		2-[2-(3-fluoro-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
410		2-[2-(2-chloro-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
411		2-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
412		2-[2-(2-amino-3,5-dichlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

413		2-[3-(2-bromo-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
414		1-(4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl)-2-phenylethane-1,2-dione	
415		2-[2-[2-(phenylthio)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
416		N-butyl-N'-[4-methyl-3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]urea	
417		2-morpholin-4-yl-N-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	
418		2-[3-(4-[[(4-bromo-3-methylphenyl)amino]methyl]phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
419		2-[2-[2-fluoro-6-[3-(trifluoromethyl)phenoxy]phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
420		4-tert-butyl-N-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]benzenesulfonamide	

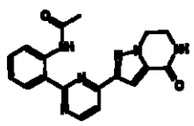
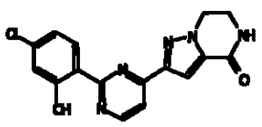
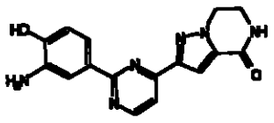
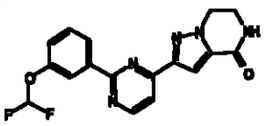
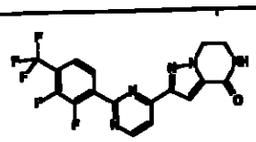
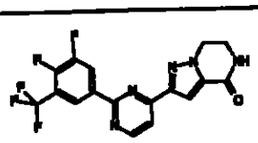
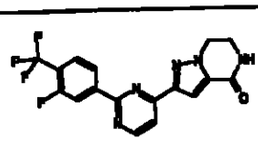
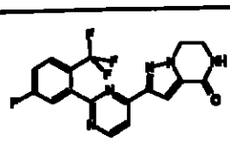
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422		2-[2-(pentachlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
423		2-[2-(4-methoxy-7-methyl-2,3-dihydro-1H-inden-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
424		2-[2-(2-amino-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
425		2-[2-(4-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
426		2-[2-(2-chloro-3,4-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
427		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzenesulfonamide	
428		2-[2-(3,5-dibromophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

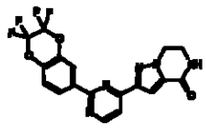
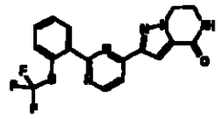
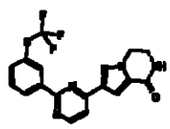
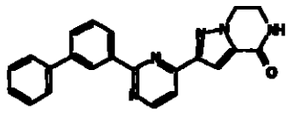
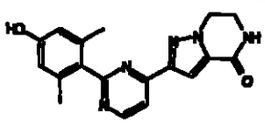
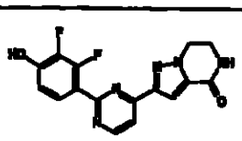
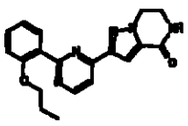
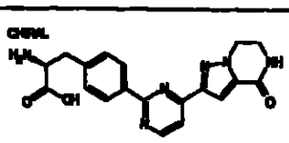
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431		2-[2-[4-chloro-3-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
432		3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenylalanine	
433		2-[2-(4'-amino-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
434		2-[2-(2-fluoro-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
435		2-[2-(4'-[[(2S)-2-methylbutyl]oxy]-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
436		N-[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-2-(trifluoromethoxy)phenyl]acetamide	

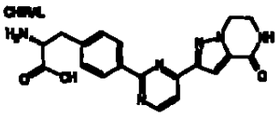
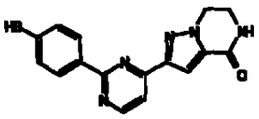
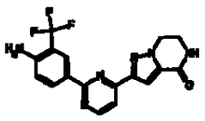
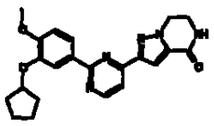
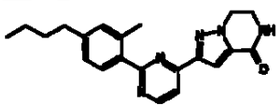
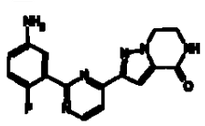
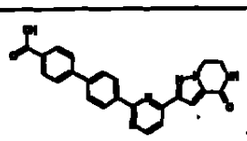
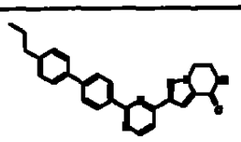
437		2-[2-(4-amino-3-(trifluoromethoxy)phenyl)pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
438		2-(2-[3-[(2-oxo-1,3-benzoxazol-3(2H)-yl)methyl]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
439		N-[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]methanesulfonamide	
440		2-[2-[2-amino-5-[1-hydroxy-2-(isopropylamino)ethyl]phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
441		2-[2-[4-(4-mercaptobenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
442		2-(2-[10-[3-(4-hydroxypiperidin-1-yl)propyl]-10H-phenothiazin-2-yl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
443		2-[2-(3-fluoro-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
444		2-[2-(3-fluoro-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

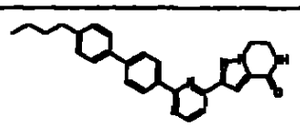
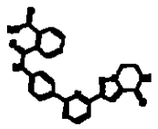
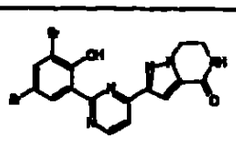
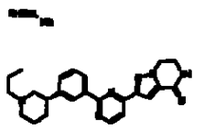
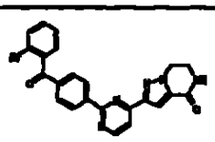
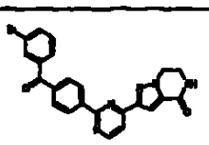
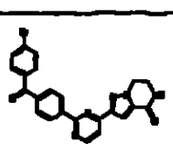
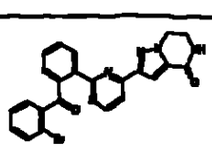
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446		2-[2-(4-pentylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
447		2-[2-(5-chloro-2-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
448		2-[2-[2,6-dichloro-4-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
449		N-[2-ethyl-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	
450		2-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
451		2-[2-[2-(difluoromethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
452		2-[2-(4-hydroxy-3,5-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

58 57

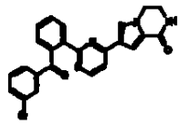
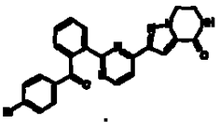
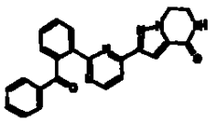
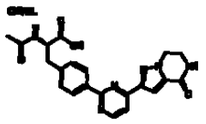
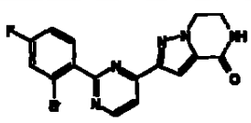
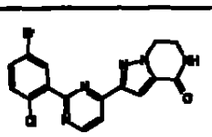
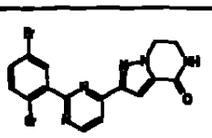
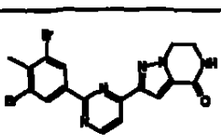
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454		2-[2-(4-chloro-2-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
455		2-[2-(3-amino-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
456		2-[2-[3-(difluoromethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
457		2-[2-[2,3-difluoro-4-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
458		2-[2-[3,4-difluoro-5-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
459		2-[2-[3-fluoro-4-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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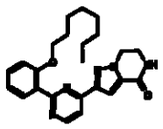
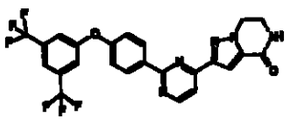
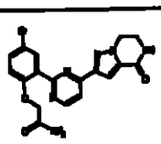
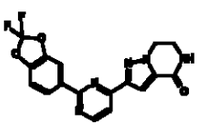
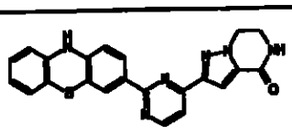
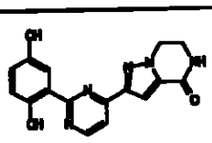
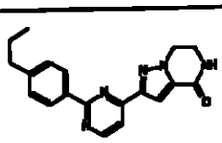
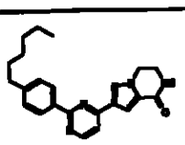
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482		2-(2-[2-[(trifluoromethyl)thio]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
483		2-(2-[3-[(trifluoromethyl)thio]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
484		2-[2-(1,1'-biphenyl-3-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
485		2-[2-(4-hydroxy-2,6-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
486		2-[2-(2,3-difluoro-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
487		2-[2-(2-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
488		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	

469		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-D-phenylalanine	
470		2-[2-(4-mercaptophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
471		2-[2-(4-amino-3-(trifluoromethyl)phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
472		2-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
473		2-[2-(4-butyl-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
474		2-[2-(5-amino-2-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
475		4'-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-1,1'-biphenyl-4-carboxylic acid	
476		2-[2-(4'-propyl-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

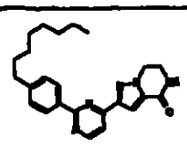
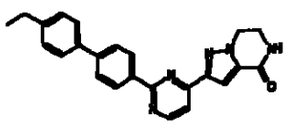
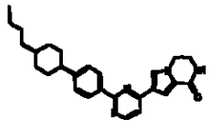
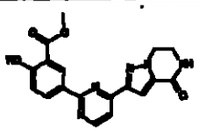
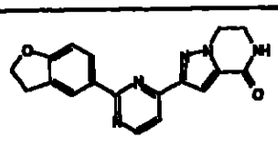
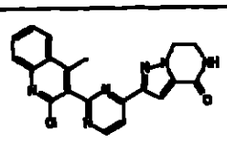
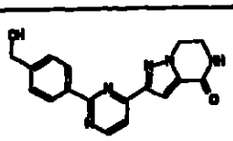
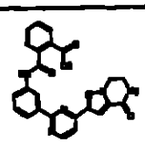
477		2-[2-(4'-butyl-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
478		2-[[[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]amino]carbonyl]benzoic acid	
479		2-[2-(3,5-dibromo-2-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
480		2-(2-[3-[(3S)-1-propylpiperidin-3-yl]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride	
481		2-[2-[4-(2-bromobenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
482		2-[2-[4-(3-bromobenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
483		2-[2-[4-(4-bromobenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
484		2-[2-[2-(2-bromobenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

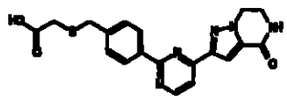
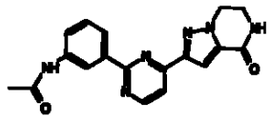
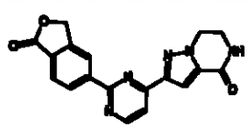
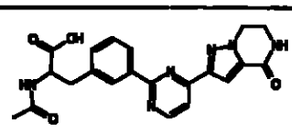
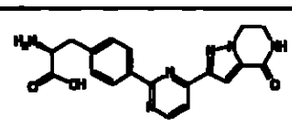
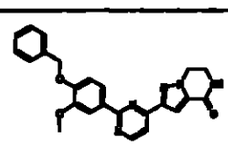
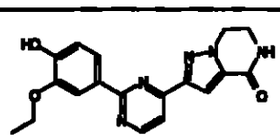
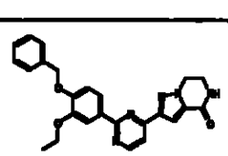
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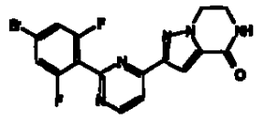
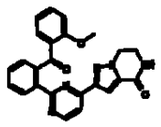
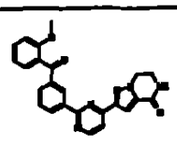
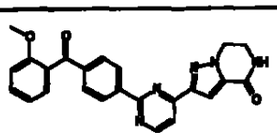
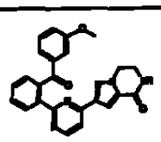
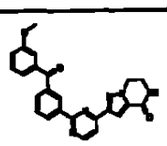
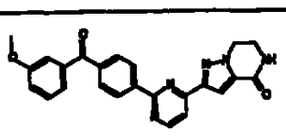
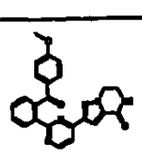
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486		2-[2-[2-(4-bromobenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
487		2-[2-[2-benzoylphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
488		N-acetyl-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	
489		2-[2-(2-bromo-4-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
490		2-[2-(5-bromo-2-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
491		2-[2-(2,5-dibromophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
492		2-[2-(3,5-dibromo-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

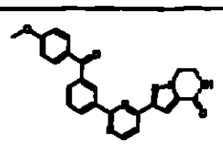
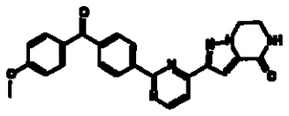
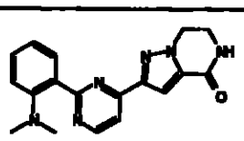
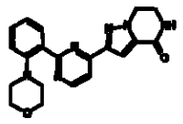
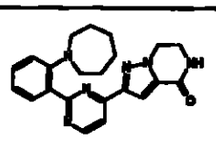
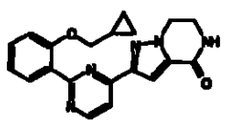
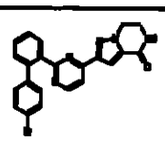
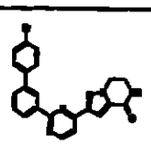
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494		2-(2-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
495		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
496		2-[2-(2,2-difluoro-1,3-benzodioxol-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
497		2-[2-(10H-phenothiazin-3-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
498		2-[2-(2,5-dihydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
499		2-[2-(4-propylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
500		2-[2-(4-hexylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

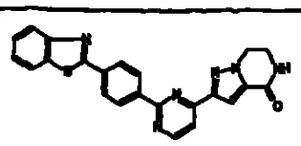
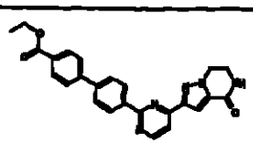
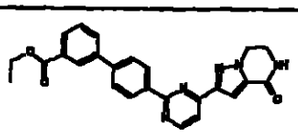
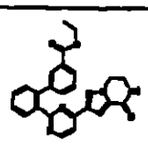
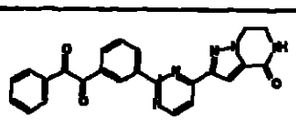
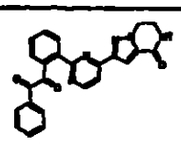
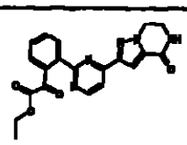
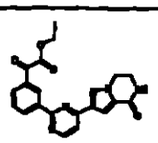
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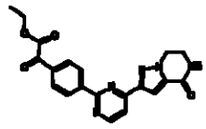
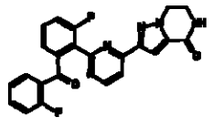
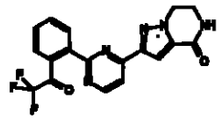
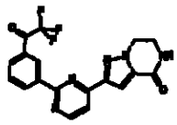
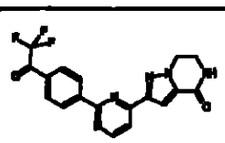
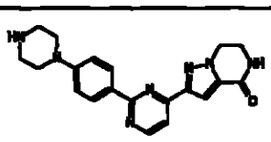
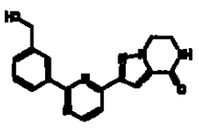
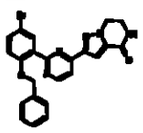
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502		2-[2-(4'-ethyl-1,1'-biphenyl-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
503		2-[2-[4-(4-butyloxycyclohexyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
504		methyl 2-hydroxy-5-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoate	
505		2-[2-(2,3-dihydro-1-benzofuran-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
506		2-[2-(2-chloro-4-methylquinolin-3-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
507		2-[2-[4-(hydroxymethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
508		2-[[[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]amino]carbonyl]benzoic acid	

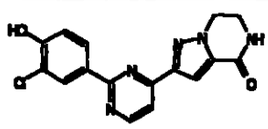
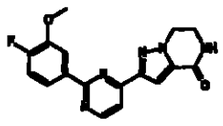
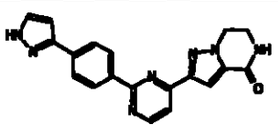
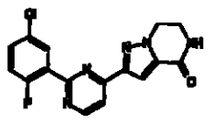
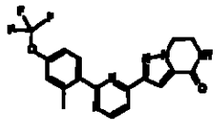
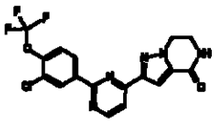
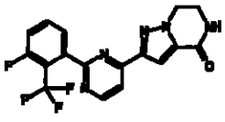
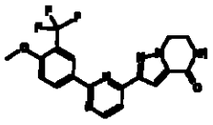
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510		N-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	
511		2-[2-(1-oxo-1,3-dihydro-2-benzofuran-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
512		N-acetyl-3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenylalanine	
513		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	
514		2-[2-[4-(benzyloxy)-3-methoxyphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
515		2-[2-(3-ethoxy-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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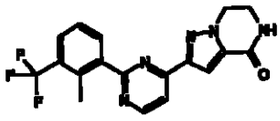
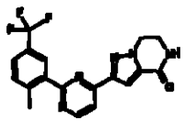
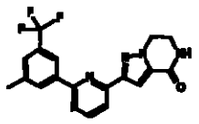
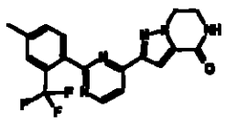
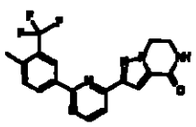
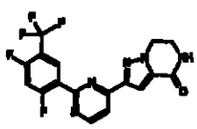
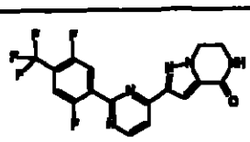
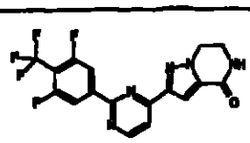
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518		2-[2-[2-(2-methoxybenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
519		2-[2-[3-(2-methoxybenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
520		2-[2-[4-(2-methoxybenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
521		2-[2-[2-(3-methoxybenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
522		2-[2-[3-(3-methoxybenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
523		2-[2-[4-(3-methoxybenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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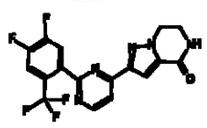
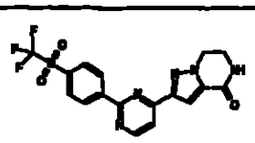
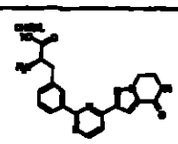
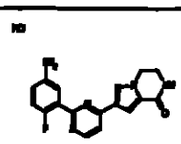
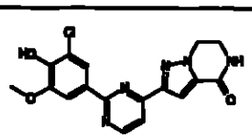
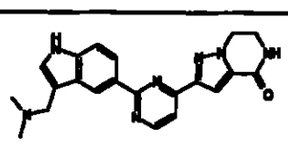
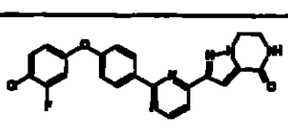
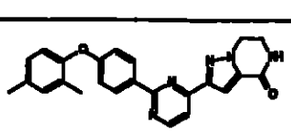
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526		2-[2-[4-(4-methoxybenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
527		2-[2-[2-(dimethylamino)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
528		2-[2-(2-morpholin-4-ylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
529		2-[2-(2-azepan-1-ylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
530		2-[2-[2-(cyclopropylmethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
531		2-[2-(4'-bromo-1,1'-biphenyl-2-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
532		2-[2-(4'-bromo-1,1'-biphenyl-3-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

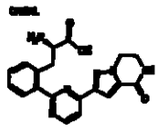
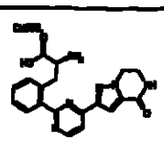
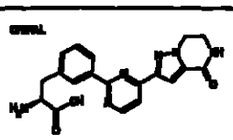
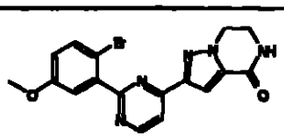
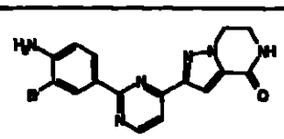
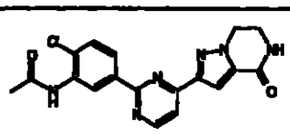
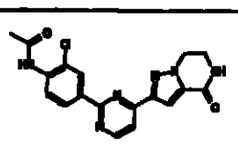
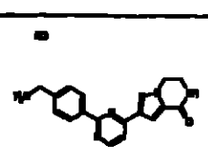
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534		ethyl 4'-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-1,1'-biphenyl-4-carboxylate	
535		ethyl 4'-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-1,1'-biphenyl-3-carboxylate	
536		ethyl 2'-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-1,1'-biphenyl-3-carboxylate	
537		1-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]-2-phenylethane-1,2-dione	
538		1-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]-2-phenylethane-1,2-dione	
539		ethyl oxo[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetate	
540		ethyl oxo[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetate	

541		ethyl oxo[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetate	
542		2-[2-[2-fluoro-6-(2-fluorobenzoyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
543		2-[2-[2-(trifluoroacetyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
544		2-[2-[3-(trifluoroacetyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
545		2-[2-[4-(trifluoroacetyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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547		2-[2-[3-(hydroxymethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
548		2-[2-[2-(benzyloxy)-5-bromophenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

548		2-[2-(3-chloro-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
550		2-[2-(4-fluoro-3-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
551		2-[2-[4-(1H-pyrazol-3-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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553		2-[2-[2-methyl-4-(trifluoromethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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555		2-[2-[3-fluoro-2-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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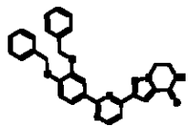
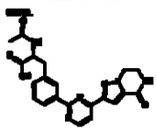
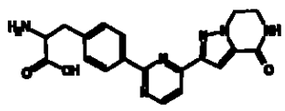
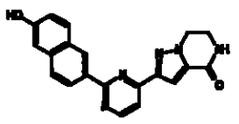
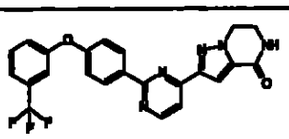
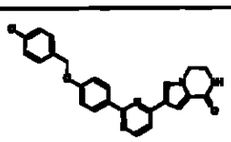
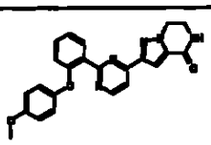
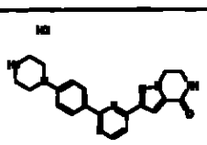
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559		2-[2-[3-methyl-5-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
560		2-[2-[4-methyl-2-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
561		2-[2-[4-methyl-3-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
562		2-[2-[2,4-difluoro-5-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
563		2-[2-[2,5-difluoro-4-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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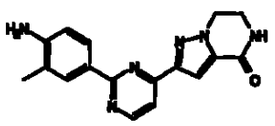
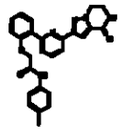
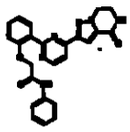
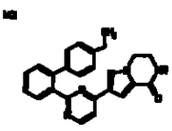
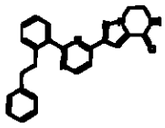
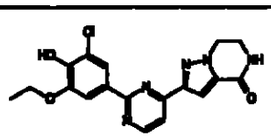
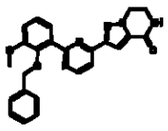
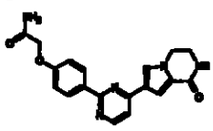
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568		2-(2-[4-[(trifluoromethyl)sulfonyl]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
567		3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-D-phenylalanine	
569		2-[2-(5-amino-2-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride	
569		2-[2-(3-chloro-4-hydroxy-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
570		2-(2-[3-[(dimethylamino)methyl]-1H-indol-5-yl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
571		2-[2-[4-(4-chloro-3-fluorophenoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
572		2-[2-[4-(2,4-dimethylphenoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

573		2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-D-phenylalanine	
574		2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	
575		3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	
576		2-[2-(3-bromo-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
577		2-[2-(4-amino-3-bromophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
578		N-[2-chloro-5-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	
579		N-[2-chloro-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	
580		2-[2-[4-(aminomethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride	

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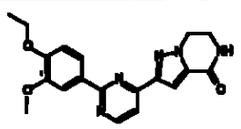
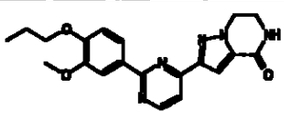
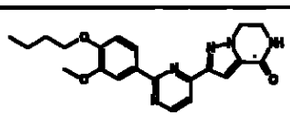
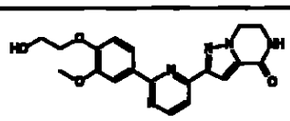
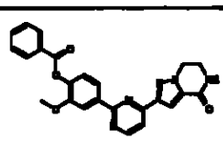
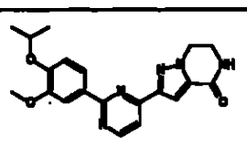
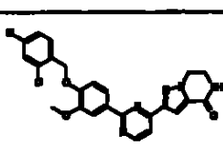
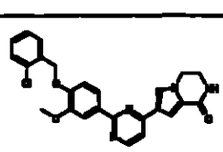
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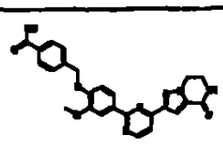
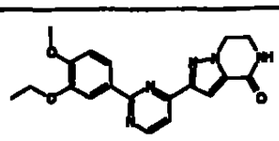
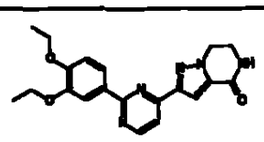
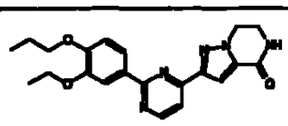
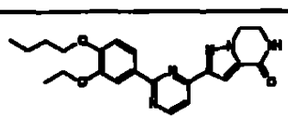
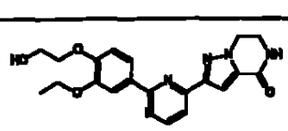
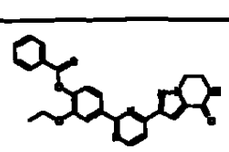
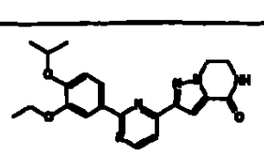
581		2-[2-[3,4-bis(benzyloxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
582		N-acetyl-3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	
583		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenylalanine	
584		2-[2-(6-hydroxy-2-naphthyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
585		2-(2-[4-[3-(trifluoromethyl)phenoxy]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
586		2-(2-[4-[(4-chlorobenzyl)oxy]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
587		2-[2-[2-(4-methoxyphenoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
588		2-[2-(4-piperazin-1-ylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride	

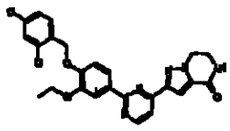
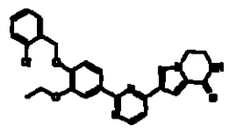
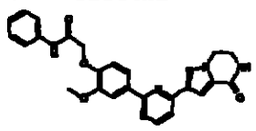
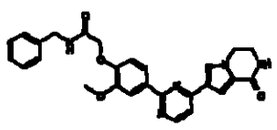
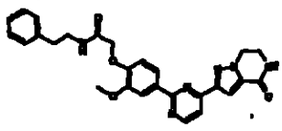
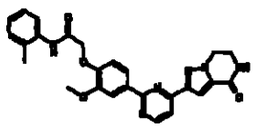
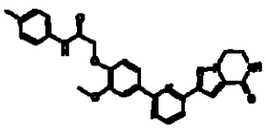
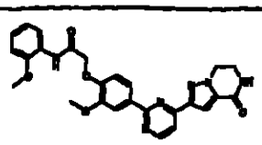
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590		N-(4-methylphenyl)-2-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
591		2-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-phenylacetamide	
592		2-[2-[4'-(aminomethyl)-1,1'-biphenyl-2-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride	
593		2-[2-[2-(2-phenylethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
594		2-[2-(3-chloro-5-ethoxy-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
595		2-[2-[2-(benzyloxy)-3-methoxyphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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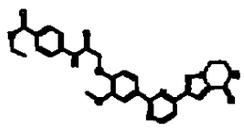
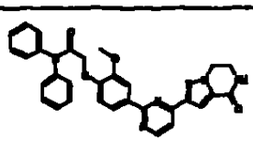
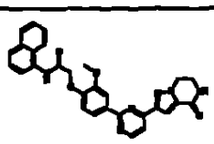
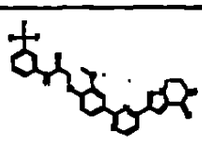
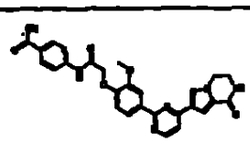
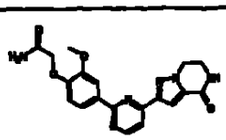
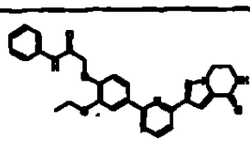
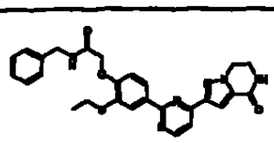
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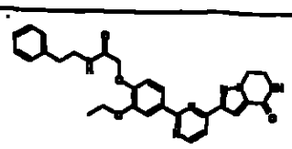
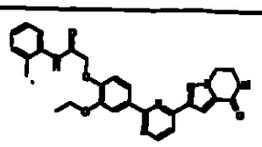
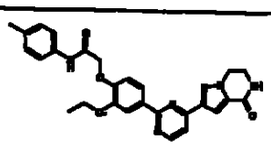
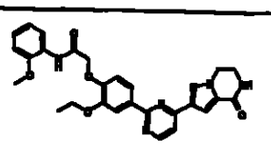
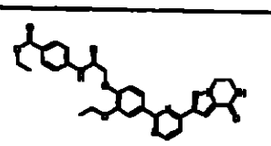
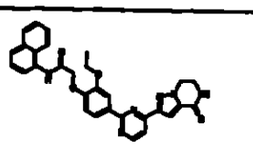
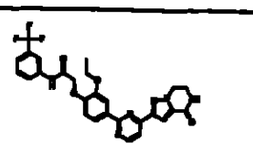
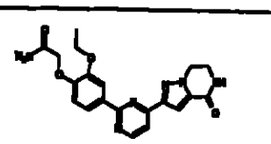
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599		2-[2-(4-butoxy-3-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
600		2-[2-[4-(2-hydroxyethoxy)-3-methoxyphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
601		2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl benzoate	
602		2-[2-(4-isopropoxy-3-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
603		2-(2-[4-[(2,4-dichlorobenzyl)oxy]-3-methoxyphenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
604		2-(2-[4-[(2-chlorobenzyl)oxy]-3-methoxyphenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

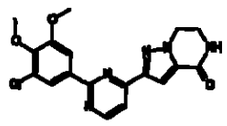
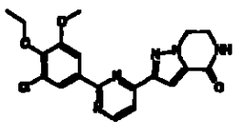
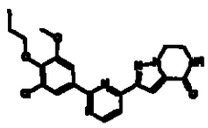
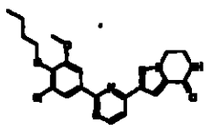
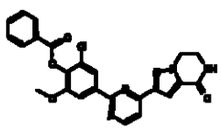
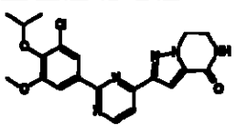
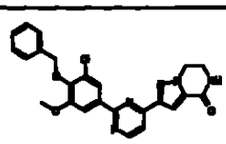
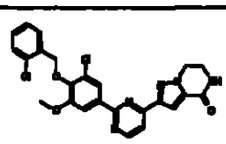
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608		2-[2-(3-ethoxy-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
607		2-[2-(3,4-diethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
609		2-[2-(3-ethoxy-4-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
609		2-[2-(4-butoxy-3-ethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
610		2-[2-[3-ethoxy-4-(2-hydroxyethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
611		2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl benzoate	
612		2-[2-(3-ethoxy-4-isopropoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

613		2-[2-(4-[(2,4-dichlorobenzyl)oxy]-3-ethoxyphenyl)pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
614		2-(2-(4-[(2-chlorobenzyl)oxy]-3-ethoxyphenyl)pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
615		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-phenylacetamide	
616		N-benzyl-2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
617		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-phenylethyl)acetamide	
618		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methylphenyl)acetamide	
619		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(4-methylphenyl)acetamide	
620		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methoxyphenyl)acetamide	

621		ethyl 4-[({2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy}acetyl)amino]benzoate	
622		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N,N-diphenylacetamide	
623		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-1-naphthylacetamide	
624		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-[3-(trifluoromethyl)phenyl]acetamide	
625		4-[({2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy}acetyl)amino]benzoic acid	
626		2-[2-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
627		2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-phenylacetamide	
628		N-benzyl-2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	

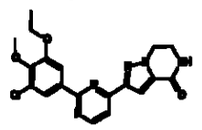
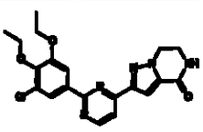
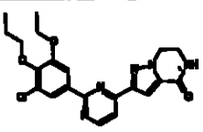
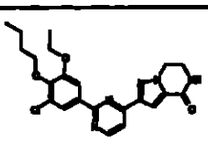
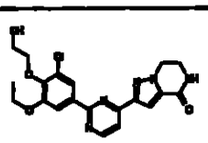
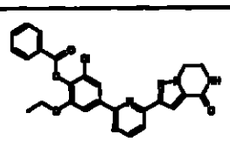
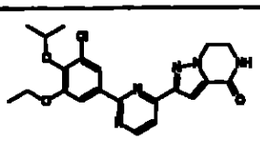
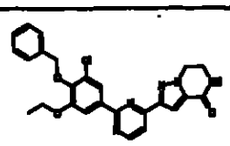
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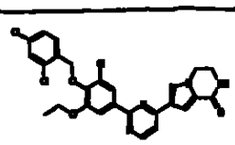
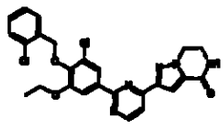
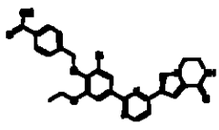
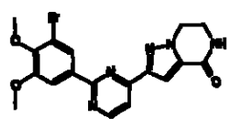
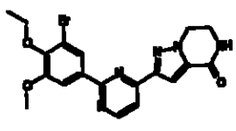
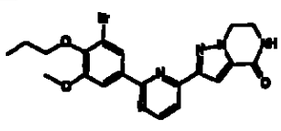
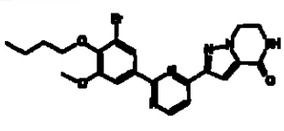
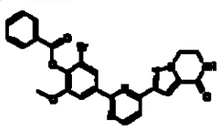
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630		2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methylphenyl)acetamide	
631		2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(4-methylphenyl)acetamide	
632		2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methoxyphenyl)acetamide	
633		ethyl 4-[({2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy}acetyl)amino]benzoate	
634		2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-1-naphthylacetamide	
635		2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-[3-(trifluoromethyl)phenyl]acetamide	
636		2-[2-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	

637		2-[2-(3-chloro-4,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
638		2-[2-(3-chloro-4-ethoxy-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
639		2-[2-(3-chloro-5-methoxy-4-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
640		2-[2-(4-butoxy-3-chloro-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
641		2-chloro-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl benzoate	
642		2-[2-(3-chloro-4-isopropoxy-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
643		2-[2-[4-(benzyloxy)-3-chloro-5-methoxyphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
644		2-(2-[3-chloro-4-[(2-chlorobenzyl)oxy]-5-methoxyphenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

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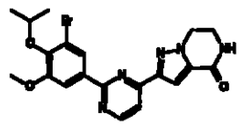
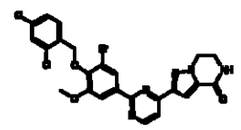
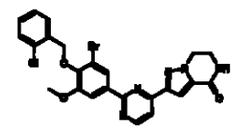
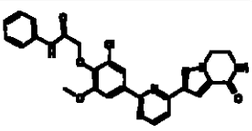
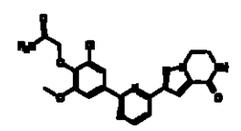
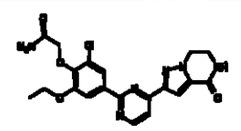
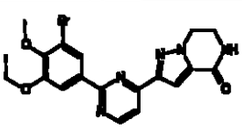
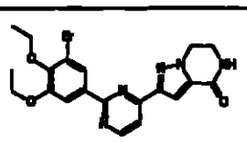
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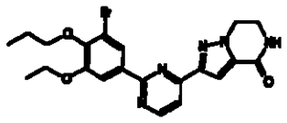
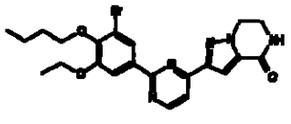
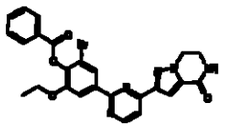
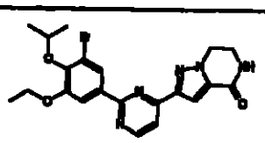
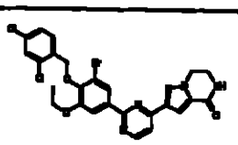
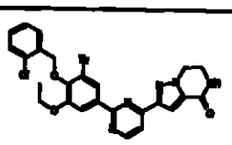
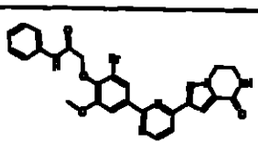
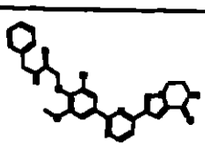
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646		2-[2-(3-chloro-4,5-diethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
647		2-[2-(3-chloro-5-ethoxy-4-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
648		2-[2-(4-butoxy-3-chloro-5-ethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
649		2-[2-(3-chloro-5-ethoxy-4-(2-hydroxyethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
650		2-chloro-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl benzoate	
651		2-[2-(3-chloro-5-ethoxy-4-isopropoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
652		2-[2-[4-(benzyloxy)-3-chloro-5-ethoxyphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

653		2-(2-[3-chloro-4-[(2,4-dichlorobenzyl)oxy]-5-ethoxyphenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
654		2-(2-[3-chloro-4-[(2-chlorobenzyl)oxy]-5-ethoxyphenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
655		4-([2-chloro-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]methyl)benzoic acid	
656		2-[2-(3-bromo-4,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
657		2-[2-(3-bromo-4-ethoxy-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
658		2-[2-(3-bromo-5-methoxy-4-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
659		2-[2-(3-bromo-4-butoxy-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
660		2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl benzoate	

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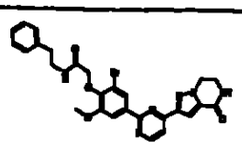
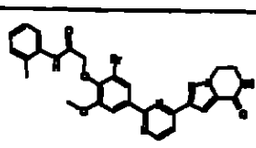
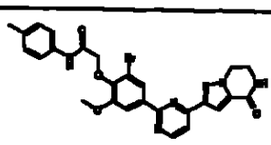
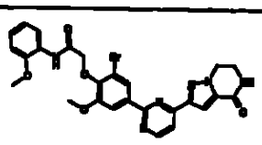
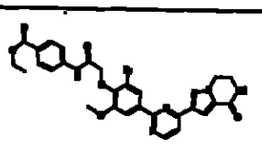
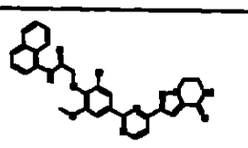
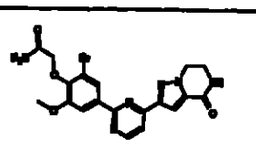
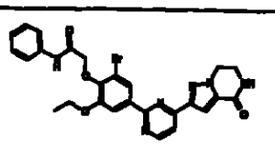
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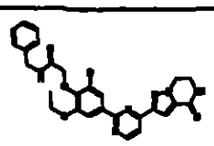
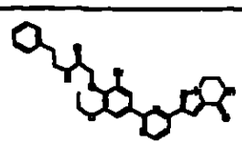
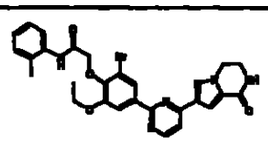
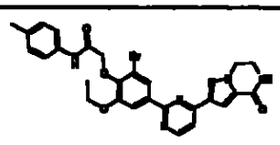
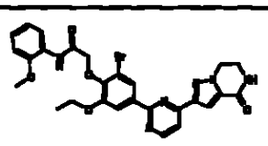
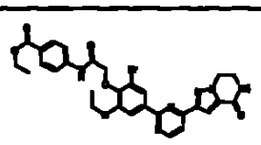
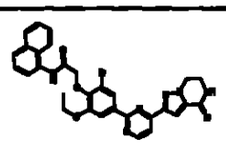
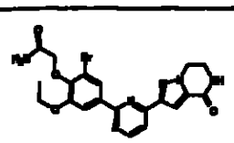
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682		2-(2-[3-bromo-4-[(2,4-dichlorobenzyl)oxy]-5-methoxyphenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
683		2-(2-[3-bromo-4-[(2-chlorobenzyl)oxy]-5-methoxyphenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
684		2-[2-chloro-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-phenylacetamide	
685		2-[2-chloro-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
686		2-[2-chloro-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
687		2-[2-(3-bromo-5-ethoxy-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
688		2-[2-(3-bromo-4,5-diethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

669		2-[2-(3-bromo-5-ethoxy-4-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
670		2-[2-(3-bromo-4-butoxy-5-ethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
671		2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl benzoate	
672		2-[2-(3-bromo-5-ethoxy-4-isopropoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
673		2-[2-(3-bromo-4-[(2,4-dichlorobenzyl)oxy]-5-ethoxyphenyl)pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
674		2-(2-(3-bromo-4-[(2-chlorobenzyl)oxy]-5-ethoxyphenyl)pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
675		2-[2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-phenylacetamide	
676		N-benzyl-2-[2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	

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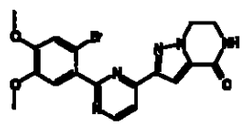
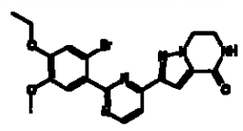
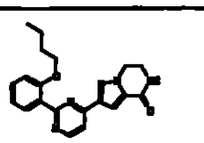
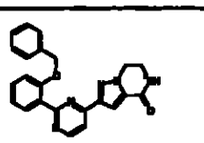
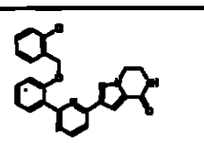
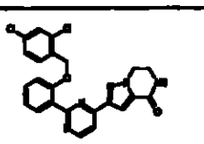
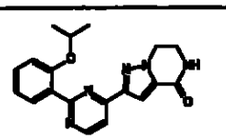
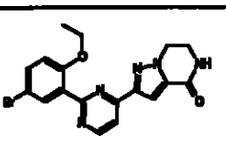
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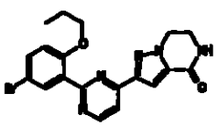
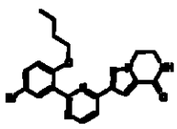
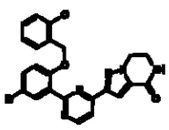
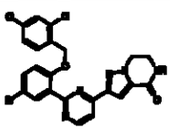
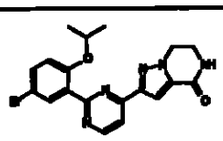
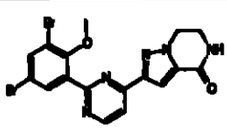
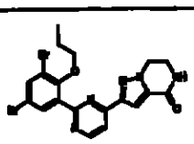
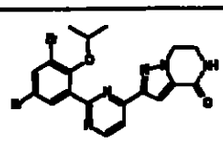
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678		2-[2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methylphenyl)acetamide	
679		2-[2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(4-methylphenyl)acetamide	
680		2-[2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methoxyphenyl)acetamide	
681		ethyl 4-[([2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetyl)amino]benzoate	
682		2-[2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-1-naphthylacetamide	
683		2-[2-bromo-6-methoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
684		2-[2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-phenylacetamide	

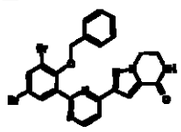
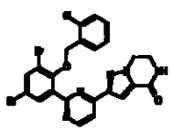
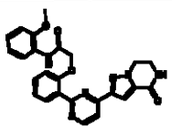
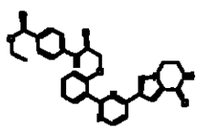
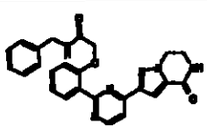
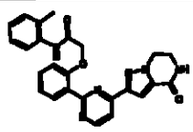
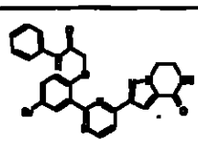
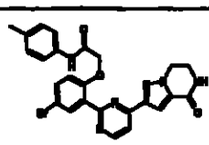
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686		2-[2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-phenylethyl)acetamide	
687		2-[2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methylphenyl)acetamide	
688		2-[2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(4-methylphenyl)acetamide	
689		2-[2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methoxyphenyl)acetamide	
690		ethyl 4-[((2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy)acetyl)amino]benzoate	
691		2-[2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-1-naphthylacetamide	
692		2-[2-bromo-6-ethoxy-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	

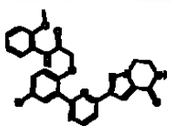
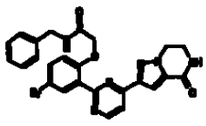
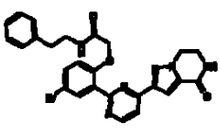
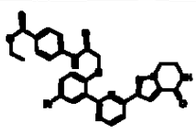
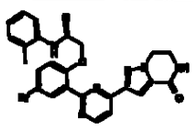
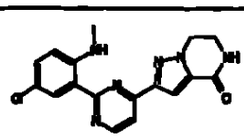
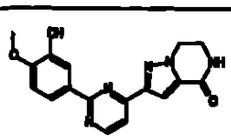
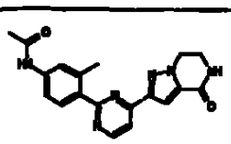
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693		2-[2-(2-bromo-4,5-dimethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
694		2-[2-(2-bromo-4-ethoxy-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
695		2-[2-(2-butoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
696		2-[2-[2-(benzyloxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
697		2-(2-[2-[(2-chlorobenzyl)oxy]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
698		2-(2-[2-[(2,4-dichlorobenzyl)oxy]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
699		2-[2-(2-isopropoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
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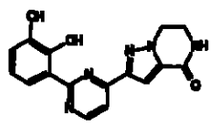
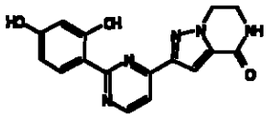
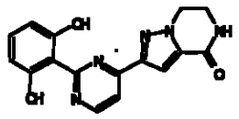
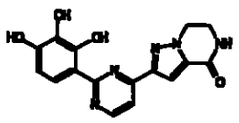
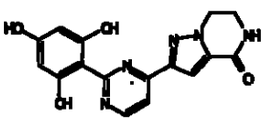
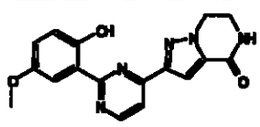
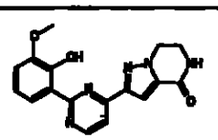
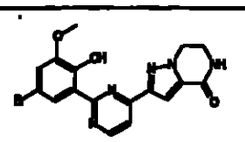
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702		2-[2-(5-bromo-2-butoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
703		2-(2-[5-bromo-2-[(2-chlorobenzyl)oxy]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
704		2-(2-[5-bromo-2-[(2,4-dichlorobenzyl)oxy]phenyl]pyrimidin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
705		2-[2-(5-bromo-2-isopropoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
706		2-[2-(3,5-dibromo-2-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
707		2-[2-(3,5-dibromo-2-propoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
708		2-[2-(3,5-dibromo-2-isopropoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

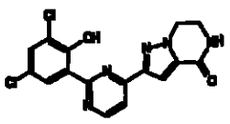
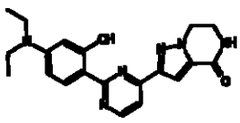
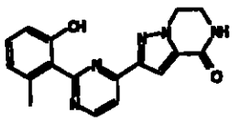
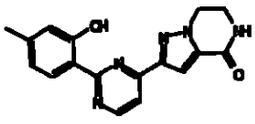
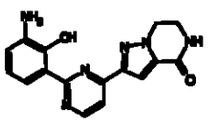
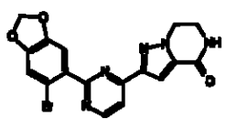
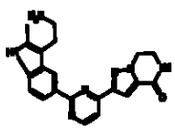
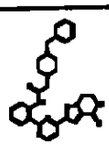
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710		2-[2-[3,5-dibromo-2-[(2-chlorobenzyl)oxy]phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
711		N-(2-methoxyphenyl)-2-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
712		ethyl 4-[[(2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetyl]amino]benzoate	
713		N-benzyl-2-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
714		N-(2-methylphenyl)-2-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
715		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-phenylacetamide	
716		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(4-methylphenyl)acetamide	

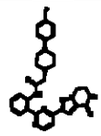
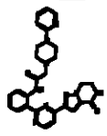
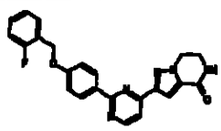
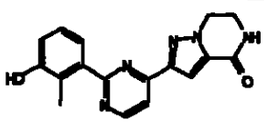
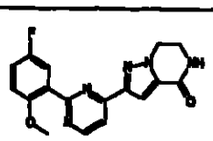
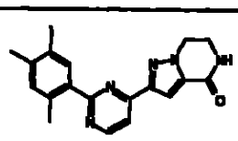
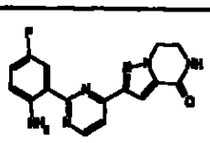
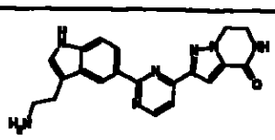
717		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-methoxyphenyl)acetamide	
718		N-benzyl-2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetamide	
719		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(2-phenylethyl)acetamide	
720		ethyl 4-[([4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]acetyl)amino]benzoate	
721		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenoxy]-N-(3-methylphenyl)acetamide	
722		2-[2-[5-chloro-2-(methylamino)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
723		2-[2-(3-hydroxy-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
724		N-[3-methyl-4-(4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	

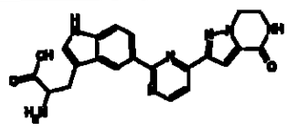
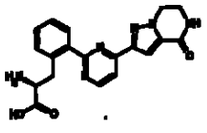
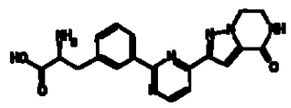
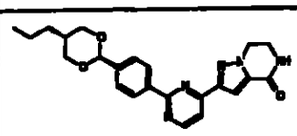
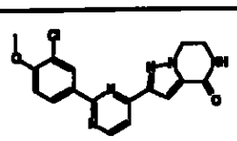
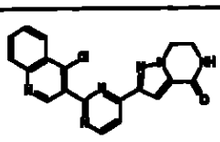
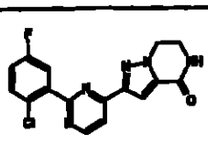
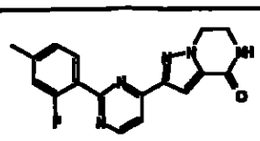
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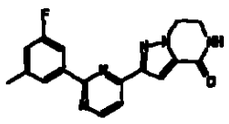
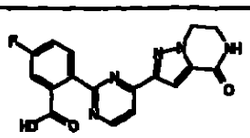
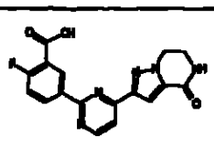
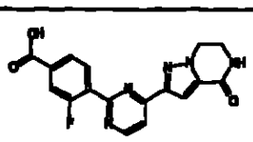
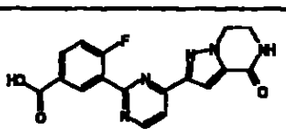
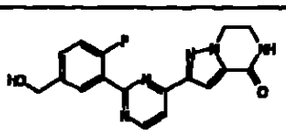
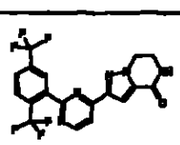
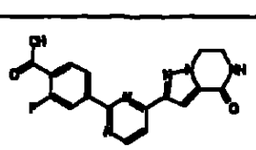
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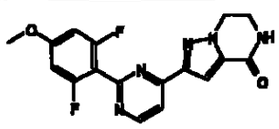
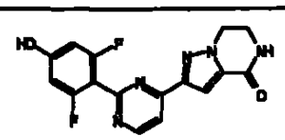
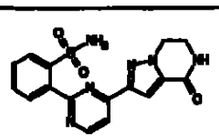
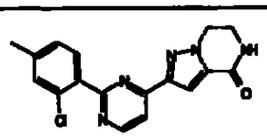
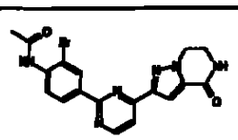
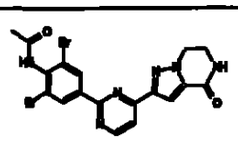
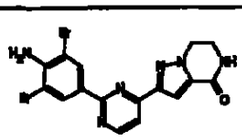
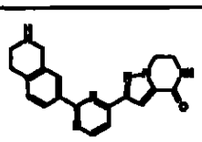
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727		2-[2-(2,6-dihydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
728		2-[2-(2,3,4-trihydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
729		2-[2-(2,4,6-trihydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
730		2-[2-(2-hydroxy-5-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
731		2-[2-(2-hydroxy-3-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
732		2-[2-(5-bromo-2-hydroxy-3-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

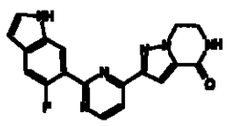
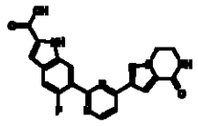
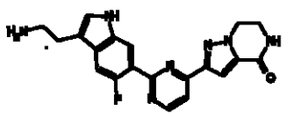
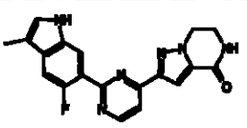
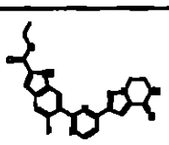
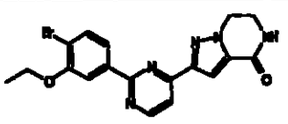
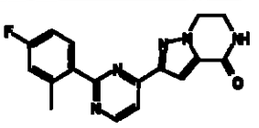
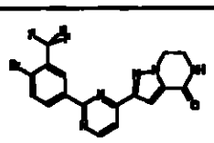
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734		2-[2-[4-(diethylamino)-2-hydroxyphenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
735		2-[2-(2-hydroxy-6-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
736		2-[2-(2-hydroxy-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
737		2-[2-(3-amino-2-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
738		2-[2-(6-bromo-1,3-benzodioxol-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
739		2-[2-[3-(2-aminoethyl)-2-methyl-1H-indol-5-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
740		2-(4-benzylpiperazin-1-yl)-N-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]pyrimidin-2-yl]phenyl]acetamide	

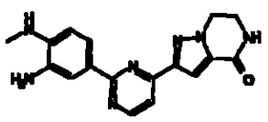
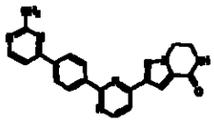
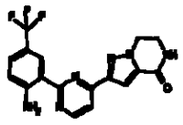
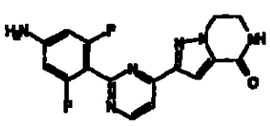
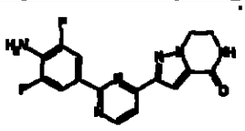
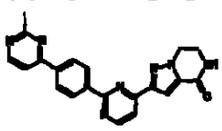
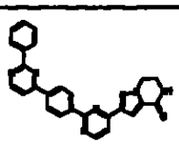
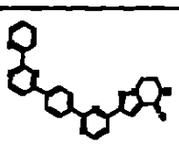
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742		N-[2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]-2-(4-pyridin-2-ylpiperazin-1-yl)acetamide	
743		2-[2-[4-[(2-fluorobenzyl)oxy]phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
744		2-[2-(3-hydroxy-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
745		2-[2-(5-fluoro-2-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
746		2-[2-(2,4,5-trimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
747		2-[2-(2-amino-5-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
748		2-[2-[3-(2-aminoethyl)-1H-indol-5-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

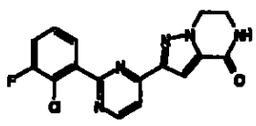
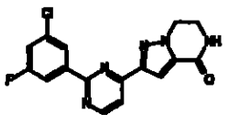
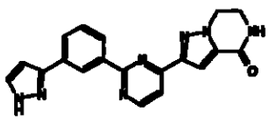
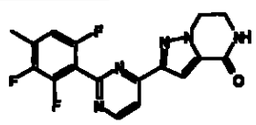
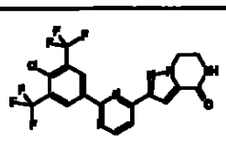
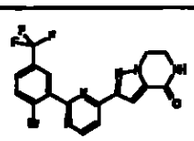
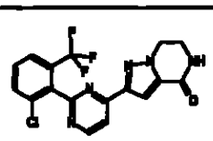
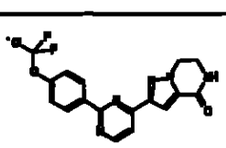
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750		2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	
751		3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-L-phenylalanine	
752		2-[2-[4-(5-propyl-1,3-dioxan-2-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
753		2-[2-(3-chloro-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
754		2-[2-(4-chloroquinolin-3-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
755		2-[2-(2-chloro-6-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
756		2-[2-(2-fluoro-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

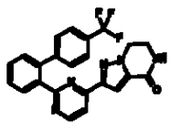
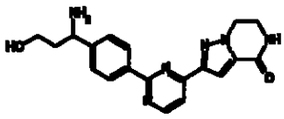
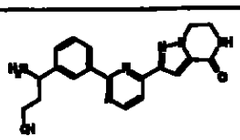
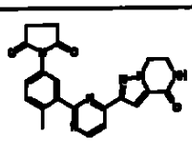
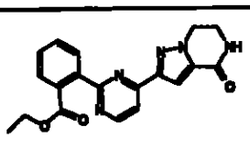
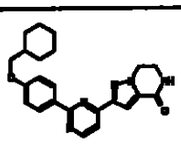
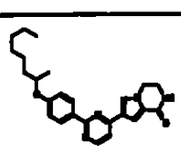
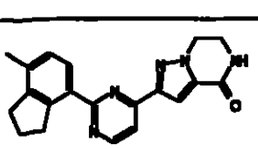
757		2-[2-(3-fluoro-5-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
758		5-fluoro-2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
759		2-fluoro-5-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
760		3-fluoro-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
761		4-fluoro-3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	
762		2-[2-[2-fluoro-5-(hydroxymethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
763		2-[2-[3,5-bis(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
764		2-fluoro-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoic acid	

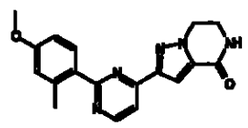
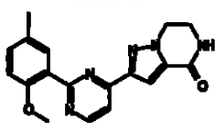
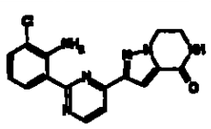
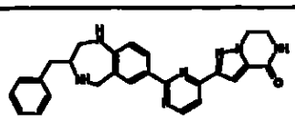
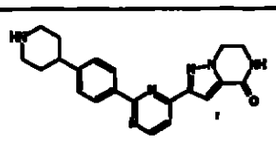
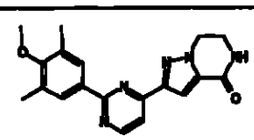
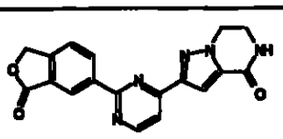
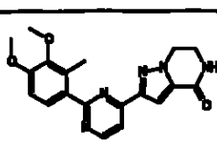
765		2-[2-(2,6-difluoro-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
766		2-[2-(2,6-difluoro-4-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
767		2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzenesulfonamide	
768		2-[2-(2-chloro-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
769		N-[2-bromo-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	
770		N-[2,6-dibromo-4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]acetamide	
771		2-[2-(4-amino-3,5-dibromophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
772		2-[2-(1,2,3,4-tetrahydroisoquinolin-7-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

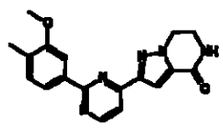
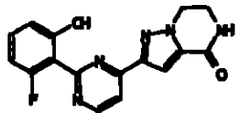
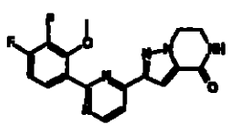
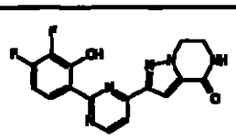
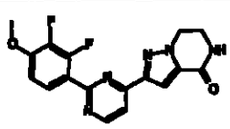
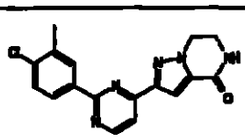
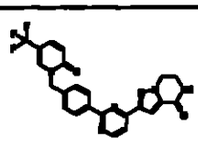
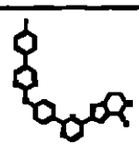
773		2-[2-(5-fluoro-1H-indol-6-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
774		5-fluoro-6-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-1H-indole-2-carboxylic acid	
776		2-[2-[3-(2-aminoethyl)-5-fluoro-1H-indol-6-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
776		2-[2-(5-fluoro-3-methyl-1H-indol-6-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
777		ethyl 5-fluoro-6-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-1H-indole-2-carboxylate	
778		2-[2-(4-bromo-3-ethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
779		2-[2-(4-fluoro-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
780		2-[2-[4-bromo-3-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

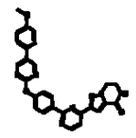
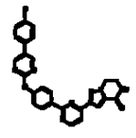
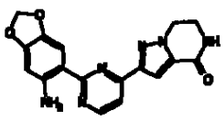
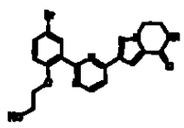
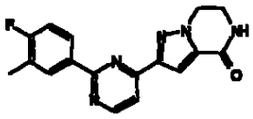
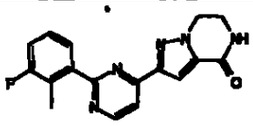
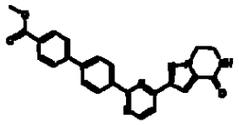
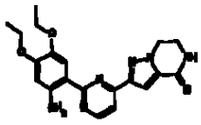
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782		2-[2-[4-(2-aminopyrimidin-4-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
783		2-[2-[2-amino-5-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
784		2-[2-(4-amino-2,6-difluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
785		2-[2-(4-amino-3,5-difluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
786		2-[2-[4-(2-methylpyrimidin-4-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
787		2-[2-[4-(2-phenylpyrimidin-4-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
788		2-[2-[4-(2-pyridin-2-ylpyrimidin-4-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

789		2-[2-(2-chloro-3-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
790		2-[2-(3-chloro-5-fluorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
791		2-[2-[3-(1H-pyrazol-3-yl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
792		2-[2-(2,3,5-trifluoro-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
793		2-[2-[4-chloro-3,5-bis(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
794		2-[2-[2-bromo-5-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
795		2-[2-[2-chloro-6-(trifluoromethyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
796		2-[2-(4-[chloro(difluoro)methoxy]phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

797		2-[2-[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
798		2-[2-[4-(1-amino-3-hydroxypropyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
799		2-[2-[3-(1-amino-3-hydroxypropyl)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
800		1-[4-methyl-3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]phenyl]pyrrolidine-2,5-dione	
801		ethyl 2-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]benzoate	
802		2-[2-[4-(cyclohexylmethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
803		2-[2-[4-[(1-methylheptyl)oxy]phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
804		2-[2-(7-methyl-2,3-dihydro-1H-inden-4-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

806		2-[2-(4-methoxy-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
808		2-[2-(2-methoxy-6-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
807		2-[2-(2-amino-6-chlorophenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
808		2-[2-(3-benzyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-7-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
809		2-[2-(4-piperidin-4-ylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
810		2-[2-(4-methoxy-3,5-dimethylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
811		2-[2-(3-oxo-1,3-dihydro-2-benzofuran-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
812		2-[2-(3,4-dimethoxy-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

813		2-[2-(3-methoxy-4-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
814		2-[2-(2-fluoro-6-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
815		2-[2-(3,4-difluoro-2-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
816		2-[2-(3,4-difluoro-2-hydroxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
817		2-[2-(2,3-difluoro-4-methoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
818		2-[2-(4-chloro-3-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
819		2-[2-(4-[(2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)methyl]phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
820		2-[2-(4-[[5-(4-methylphenyl)pyrimidin-2-yl]oxy]phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

821		2-[2-(4-[[5-(4-methoxyphenyl)pyrimidin-2-yl]oxy]phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
822		2-[2-(4-[[5-(4-fluorophenyl)pyrimidin-2-yl]oxy]phenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
823		2-[2-(6-amino-1,3-benzodioxol-5-yl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
824		2-[2-[5-bromo-2-(2-hydroxyethoxy)phenyl]pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
825		2-[2-(4-fluoro-3-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
826		2-[2-(3-fluoro-2-methylphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
827		methyl 4'-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyrimidin-2-yl]-1,1'-biphenyl-4-carboxylate	
828		2-[2-(2-amino-4,5-diethoxyphenyl)pyrimidin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	

Notes:

a) Chemical names were generated by ACD/Name software.

b) The MK-2 inhibiting compound may be shown with a solvent, such as, for example, trifluoroacetate, with which it can form a salt. Both the salt and base forms of each compound are included in the present invention.

[00039] In one embodiment of the present invention, the MK-2 inhibiting compound is one that is listed in Table I.

[00040] In another embodiment of the present invention, the MK-2 inhibiting compound is one that is listed in Table 1 or in Table 2.

[00041] In yet another embodiment of the present invention, the MK-2 inhibiting compound is one that is listed in Table 2.

[00042] It is preferred that the MK-2 inhibiting compound is one that has an IC_{50} value for the inhibition of MK-2 that is lower than 1. By way of example, this would include the compounds in Table I numbered 1 – 56. An MK-2 IC_{50} value that is lower than 0.5 is still more preferred (examples of these compounds include the compounds in Table I numbered 1 – 32), lower than 0.1 is even more preferred yet (examples of these compound include the compounds in Table I numbered 1 – 7).

[00043] In one embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except when Z^2 and Z^3 are both nitrogen, R^4 is other than pyrrole, or optionally when Z^4 and Z^5 are both nitrogen and R^a is ring Q, Q^2 is other than nitrogen.

[00044] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is selected from an M-ring or a Q-ring.

[00045] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring.

[00046] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring wherein ring M is an aromatic pyridine or pyrimidine ring, wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 and M^6 are independently selected from carbon and nitrogen and if M^2 and/or M^6 is carbon, the carbon is substituted with $(L)_nR^1$.

[00047] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring wherein ring M is an aromatic pyridine or pyrimidine ring,

wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 and M^6 are independently selected from carbon and nitrogen and if M^2 and/or M^6 is carbon, the carbon is substituted with $(L)_nR^1$; and

[00048] R^3 and R^4 optionally join to form a ring of 5, 6, 7, or 8 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

[00049] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring wherein ring M is an aromatic pyridine or pyrimidine ring, wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$; and

[00050] R^3 and R^4 optionally join to form a ring of 6 or 7 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, C=O, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

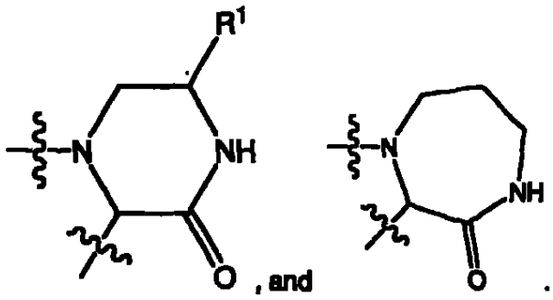
[00051] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring, wherein ring M is an aromatic pyridine or pyrimidine ring, wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$; and

[00052] R^3 and R^4 optionally join to form a ring of 6 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, C=O, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

[00053] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring wherein ring M is an aromatic pyridine or pyrimidine ring, wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is

carbon, M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$; and

R^3 and R^4 optionally join to form a ring that is selected from:



, and .

[00054] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring, wherein ring M is an aromatic pyridine ring, wherein M^1, M^3, M^4 and M^6 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 is nitrogen.

[00055] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring, wherein ring M is an aromatic pyrimidine ring, wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 and M^6 are nitrogen.

[00056] In another embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring wherein ring M is an aromatic pyridine ring, wherein:

M^1, M^3, M^4 and M^6 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon;

M^2 is nitrogen;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl-R^{11}, C_1-C_8 alkoxy-R^{11}, COR^{17}, COR_8, CO_2R_8, $CONHR_8$, $N(R^9)_2$, amino C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl-R^7, C_1-C_8 alkyl-NHR^7, carbonitrile, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_8 alkyl, NR^8R^9-C_1-C_8 alkyl, nitro, cyano, O-R^{10}, C_1-C_4 alkyl-OR^{10}, C_1-C_8 alkyl-COR^{11}, halo C_1-C_4 alkyl, aryl, heteroaryl,

heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7, R^8, are each independently selected from -H, C_1-C_8 alkyl, C_1-C_4 alkyl-R^{11}, C_1-C_8 alkyl-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, aryl, and arylalkyl, wherein aryl and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^9, R^{10} are each independently selected from -H, hydroxyl, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{17}, C_1-C_8 alkyl-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_8 alkyl-CO_2R^{16}, C_1-C_8 alkyl-CONH-R^{16}, C_1-C_8 alkyl-$CON(R^{16})_2$, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkoxy, halo C_1-C_4 alkyl, $Si(R^{13})_2R^{17}$, aryl, heteroaryl, heterocyclyl, arylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxyl, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, wherein heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, hydroxyl, oxo, C_1-C_8 alkyl, hydroxyl C_1-C_8 alkyl-R^{11}, C_1-C_{10} alkoxy, amino, amino C_1-C_4 alkyl-R^7, NHR^7, $N(R^7)_2$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NHR^8R^9, C_1-C_8 alkyl-$N(R^8)_2$, C_1-C_8 alkyl-R^{11}, C_1-C_8 alkyl-$CO_2R^7R^{11}$, C_1-C_8 alkoxy-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_8 alkyl-SR^{10}, halo, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, COR^{29}, and aryl;

R^{15}, R^{16} are each independently selected from -H, aryl, arylalkyl, wherein aryl, arylalkyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{18}, NHR^{18}, aryl, heteroarylalkyl, and heterocyclylalkyl, wherein aryl is optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, hydroxyl, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, amino, amino C_1-C_8 alkyl, $N(R^{19})_2$, C_1-C_8 alkyl-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, heteroaryl, heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are each independently selected from –H and C_1-C_8 alkyl;

R^{23} is selected from –H and C_1-C_8 alkyl;

R^{24} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, CO_2R^{29}, halo, and halo C_1-C_4 alkyl;

R^{29} is selected from -H, and C_1-C_8 alkyl;

R^{30} is selected from -H, aryl, heteroaryl, heterocyclyl, alkylaryl, arylalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{36};

R^{36} is selected from –H and halo; and

R^2, R^3, R^4, R^{37} and R^{38} are each independently selected from an R^1 group.

[00057] In an embodiment of the present invention, the MK-2 inhibiting compound is one having the structure of formula I, except that R^a is an M-ring wherein ring M is an aromatic pyrimidine ring, wherein:

M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon;

M^2 and M^6 are nitrogen;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl-R^{11}, C_1-C_8 alkoxy-R^{11}, COR^{17}, COR_8, CO_2R_8, $CONHR_8$, $N(R^8)_2$, amino C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl-R^7, halo C_1-C_4 alkyl, C_1-C_8 alkyl-NHR^7, carbonitrile, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_8 alkyl, NR^8R^9-C_1-C_8 alkyl, nitro, cyano, O-R^{10}, C_1-C_4 alkyl-OR^{10}, C_1-C_8 alkyl-COR^{11}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7, R^8, are each independently selected from -H, C_1-C_8 alkyl, C_1-C_4 alkyl-R^{11}, C_1-C_8 alkyl-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, aryl, and arylalkyl, wherein aryl and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^9, R^{10} are each independently selected from -H, hydroxyl, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{17}, C_1-C_8 alkyl-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_8 alkyl-CO_2R^{16}, C_1-C_8 alkyl-CONH-R^{18}, C_1-C_8 alkyl-$CON(R^{18})_2$, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkoxy, halo C_1-C_4 alkyl, $Si(R^{13})_2R^{17}$, aryl, heteroaryl, heterocyclyl, arylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxyl, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, wherein heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, hydroxyl, oxo, C_1-C_8 alkyl, hydroxyl C_1-C_8 alkyl-R^{11}, C_1-C_{10} alkoxy, amino, amino C_1-C_4 alkyl-R^7, NHR^7, $N(R^7)_2$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NHR^8R^9, C_1-C_8 alkyl-$N(R^8)_2$, C_1-C_8 alkyl-R^{11},

C_1-C_8 alkyl-$CO_2R^7R^{11}$, C_1-C_8 alkoxy-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_8 alkyl-SR^{10}, halo, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, COR^{23}, and aryl;

R^{15}, R^{16} are each independently selected from -H, aryl, arylalkyl, wherein aryl, arylalkyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{19}, NHR^{19}, aryl, heteroarylalkyl, and heterocyclylalkyl, wherein aryl is optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, hydroxyl, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, amino, amino C_1-C_8 alkyl, $N(R^{19})_2$, C_1-C_8 alkyl-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, heteroaryl, heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are each independently selected from –H and C_1-C_8 alkyl;

R^{23} is selected from –H and C_1-C_8 alkyl;

R^{24} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, CO_2R^{29}, halo, and halo C_1-C_4 alkyl;

R^{29} is selected from -H, and C_1-C_8 alkyl;

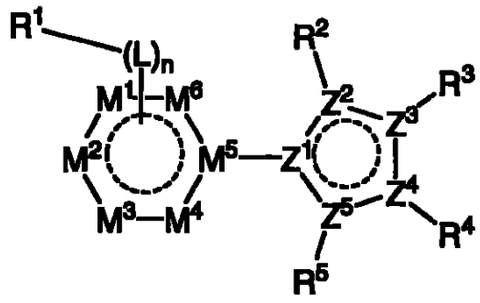
R^{30} is selected from -H, aryl, heteroaryl, heterocyclyl, alkylaryl, arylalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{36};

R^{36} is selected from –H and halo; and

R^2, R^3, R^4, R^{37} and R^{38} are each independently selected from an R^1 group.

[00058] In another embodiment, the present MK-2 inhibiting compound has the structure shown in formula III:

Formula III:



wherein:

dashed lines indicate optional single or double bonds;

Z^2 and Z^3 are nitrogen, Z^1, Z^4 and Z^5 are carbon, and join with Z^2 and Z^3 to form a pyrazole ring;

where dashed lines indicate optional single or double bonds;

M^1, M^3 and M^4 is carbon and is substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2 and M^6 is independently selected from nitrogen and carbon, and if carbon, it is unsubstituted or substituted with $(L)_nR^1$;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl-R^{11}, C_1-C_8 alkoxy-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl-R^7, halo C_1-C_4 alkyl, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-$N(R^7)_2$, carbonitrile, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_8 alkyl, NR^8R^9-C_1-C_8 alkyl, nitro, cyano, O-R^{10}, C_1-C_4 alkyl-OR^{10}, C_1-C_8 alkyl-COR^{11}, aryl,

heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7 and R^9 are each independently selected from -H, C_1-C_6 alkyl, C_1-C_4 alkyl-R^{11}, C_1-C_6 alkyl-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, aryl, and arylalkyl, wherein aryl and arylalkyl, are optionally subetituted with one or more of the groups defined by R^{18};

R^9 and R^{10} are each independently selected from -H, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkyl-R^{17}, C_1-C_6 alkyl-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alkyl-CO_2R^{16}, C_1-C_6 alkyl-$CONH$-R^{16}, C_1-C_6 alkyl-$CON(R^{16})_2$, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkoxy, halo C_1-C_4 alkyl, $Si(R^{13})_2R^{17}$, aryl, heteroaryl, heterocyclyl, arylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, wherein heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, hydroxyl, oxo, C_1-C_6 alkyl, hydroxyl C_1-C_6 alkyl-R^{11}, C_1-C_{10} alkoxy, amino, amino C_1-C_4 alkyl-R^7, NHR^7, $N(R^7)_2$, C_1-C_6 alkyl-NHR^7, C_1-C_6 alkyl-NHR^8R^9, C_1-C_6 alkyl-$N(R^9)_2$, C_1-C_6 alkyl-R^{11}, C_1-C_6 alkyl-$CO_2R^7R^{11}$, C_1-C_6 alkoxy-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_6 alkyl-SR^{10}, halo, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally subetituted with one or more of the groups defined by R^{18};

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R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, COR^{23}, and aryl;

R^{15} and R^{16} are each independently selected from -H, aryl, arylalkyl, wherein aryl, arylalkyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{19}, NHR^{19}, aryl, heteroarylalkyl, and heterocyclylalkyl, wherein aryl is optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, hydroxyl, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, amino, amino C_1-C_8 alkyl, $N(R^{19})_2$, C_1-C_8 alkyl-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, heteroaryl, heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are each independently selected from –H and C_1-C_8 alkyl;

R^{23} is selected from –H and C_1-C_8 alkyl;

R^{24} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, CO_2R^{29}, halo, and halo C_1-C_4 alkyl;

R^{29} is selected from -H, and C_1-C_8 alkyl;

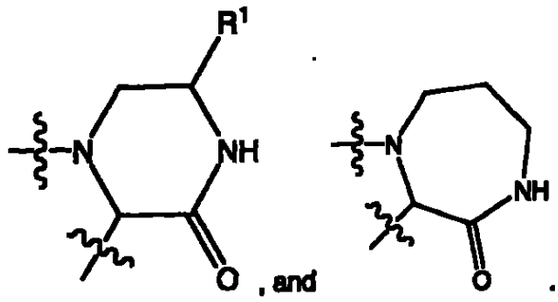
R^{30} is selected from -H, aryl, heteroaryl, heterocyclyl, alkylaryl, arylalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{38};

R^{38} is selected from –H and halo;

R^2, R^3, R^4, R^{37} and R^{38} are each independently selected from an R^1 group;

n is 0; and

R^3 and R^4 optionally join to form a ring structure that is selected from:



[00059] The MK-2 inhibiting compounds that are described in formulas I-III, and in Tables I and II can be made by the methods that are described in the Examples below. Compounds that are not described specifically in the Examples can be made by reference to the methods used in the Examples, but with the substitution of starting compounds that are suitable for the compound that is desired.

[00060] The present invention also includes a method of inhibiting mitogen activated protein kinase-activated protein kinase-2, the method comprising contacting a mitogen activated protein kinase-activated protein kinase-2 with one or more of any of the MK-2 inhibiting compounds described herein. In one embodiment, the contacting of MK-2 with an MK-2 inhibitory compound takes place inside a cell. The cell can be one of any type of organism, but is preferably an animal cell. Contacting can occur *in vitro* or *in vivo*, and the cell can be a living cell, or it can be non-living. When the contacting is carried out *in vitro*, the cell can be attached to other cells, or it can be a single cell, or clump of cells in suspension or on a solid medium. When the contacting is carried out *in vivo*, the MK-2 inhibitory compound can be administered as described below.

[00061] In one embodiment, the present invention provides a method for treating or preventing an MK-2 modulated disease or disorder in a subject, the method comprises contacting a mitogen activated protein kinase-activated protein kinase-2 in a subject with one or more of the MK-2 inhibiting compounds that are described herein. A preferred MK-2 inhibiting compound for the present method is one having the structure

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described by formula I. In another perferred embodiment, the MK-2 inhibiting compound is one having the structure described by formula II.

[00062] The present invention also includes a method of inhibiting mitogen activated protein kinase-activated protein kinase-2 in a subject in need of such inhibition, the method comprising administering to the subject one or more of the MK-2 inhibiting compounds described herein.

[00063] The present invention also includes a method of preventing or treating a TNFα mediated disease or disorder in a subject, the method comprising administering to the subject an effective amount of one or more of the MK-2 inhibiting compounds described herein. In a preferred embodiment, the subject is one that is in need of such prevention or treatment.

[00064] The present methods can be practiced by the administration of any one or more of the present MK-2 inhibiting compounds. It is preferred tht the MK-2 inhibiting compound is one having an MK-2 IC_{50} of less than about 10 μM, in an *in vitro* assay of MK-2 inhibitory activity, more preferred is a compound having an MK-2 IC_{50} of less than about 1.0 μM, yet more preferred is a compound having an MK-2 IC_{50} of less than about 0.5 μM.

[00065] It should be understood that the base forms, salts, pharmaceutically acceptable salts, and prodrugs of the compounds that are described herein, as well as isomeric forms, tautomers, racemic mixtures of the compounds, and the like, which have the same or similar activity as the compounds that are described, are to be considered to be included within the description of the compound.

[00066] The MK-2 inhibiting activity of any of the compounds described herein can be determined by any one of several methods that are well known to those having skill in the art of enzyme activity testing. One such method is described in detail in the general methods section of the examples. In addition, the efficacy of any one of the present MK-2 inhibiting compounds in therapeutic applications can be determined by

testing for inhibition of TNFα production in cell culture and in animal model assays. In general, it is preferred that the MK-2 inhibiting compounds of the present invention be capable of inhibiting the production and/or the release of TNFα in cell cultures and in animal models.

[00067] In the present method, the MK-2 inhibiting compounds that are described herein can be used as inhibitors of MAPKAP kinase-2. When this inhibition is for a therapeutic purpose, one or more of the present MK-2 inhibitory compounds can be administered to a subject that is in need of MK-2 inhibition. As used herein, a "subject in need of MK-2 inhibition" is a subject who has, or who is at risk of contracting a TNFα mediated disease or disorder. TNFα mediated diseases and disorders are described in more detail below.

[00068] As described above, in an embodiment of the present method, a subject in need of prevention or treatment of a TNFα mediated disease or disorder is treated with one or more of the present MK-2 inhibiting compounds. In one embodiment, the subject is treated with an effective amount of the MK-2 inhibiting compound. The effective amount can be an amount that is sufficient for preventing or treating the TNFα mediated disease or disorder.

[00069] The MK-2 inhibiting compound that is used in the subject method can be any MK-2 inhibiting compound that is described herein.

[00070] In the subject method, the MK-2 inhibiting compound can be used in any amount that is an effective amount. It is preferred, however, that the amount of the MK-2 inhibiting compound that is administered is within a range of about 0.1 mg/day per kilogram (kg) of the subject to about 1500 mg/day/kg. It is more preferred that the amount of the compound is within a range of about 1 mg/day/kg to about 500 mg/day/kg. An amount that is within a range of about 10 mg/day/kg to about 400 mg/day/kg, is even more preferred.

[00071] When the term "about" is used herein in relation to a dosage amount of the MK-2 inhibiting compound, it is to be understood to mean an

amount that is within ± 10% by weight of the amount or range that is described. By way of example, "about 0.1 - 10 mg/day" includes all dosages within 0.9 to 11 mg/day.

[00072] In an embodiment of the present invention, a therapeutic composition is provided that contains at least one of the MK-2 inhibiting compounds that are described herein. A preferred therapeutic composition contains a therapeutically effective amount of a compound that is described by formula I. In another embodiment, a preferred therapeutic composition is one having an MK-2 inhibiting compound that is described by formula II.

[00073] In another embodiment of the present invention, a pharmaceutical composition that contains one or more of the present MK-2 inhibitors can be administered to a subject for the prevention or treatment of a TNFα mediated disease or disorder. The pharmaceutical composition includes an MK-2 inhibitor of the present invention and a pharmaceutically acceptable carrier. A preferred MK-2 inhibitor for use in the pharmaceutical composition is described by formula I. In another embodiment, a preferred pharmaceutical composition is one having an MK-2 inhibiting compound that is described by formula II.

[00074] In another embodiment, a kit can be produced that is suitable for use in the prevention or treatment of a TNFα mediated disease or disorder. The kit comprises a dosage form comprising at least one of the MK-2 inhibitors that is described herein in an amount which comprises a therapeutically effective amount.

[00075] As used herein, an "effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is readily determined by one or ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be administered to a patient and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under

analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[00076] The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies. The phrase "therapeutically-effective" is to be understood to be equivalent to the phrase "effective for the treatment, prevention, or inhibition", and both are intended to qualify the amount of the MK-2 inhibitory compound for use in therapy which will achieve the goal of improvement in the severity of pain and inflammation and the frequency of incidence over treatment, while avoiding adverse side effects typically associated with alternative therapies.

[00077] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[00078] The frequency of dose will depend upon the half-life of the active components of the composition. If the active molecules have a short half life (*e.g.* from about 2 to 10 hours) it may be necessary to give one or more doses per day. Alternatively, if the active molecules have a long half-life (*e.g.* from about 2 to about 15 days) it may only be necessary to give a dosage once per day, per week, or even once every 1 or 2 months. A preferred dosage rate is to administer the dosage amounts described above to a subject once per day.

[00079] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be

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exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

[00080] For the purposes of calculating and expressing a dosage rate, all dosages that are expressed herein are calculated on an average amount-per-day basis irrespective of the dosage rate. For example, one 100 mg dosage of an MK-2 inhibitor taken once every two days would be expressed as a dosage rate of 50 mg/day. Similarly, the dosage rate of an ingredient where 50 mg is taken twice per day would be expressed as a dosage rate of 100 mg/day.

[00081] For purposes of calculation of dosage amounts, the weight of a normal adult human will be assumed to be 70 kg.

[00082] When the MK-2 inhibitor is supplied along with a pharmaceutically acceptable carrier, the pharmaceutical compositions that are described above can be formed. Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

[00083] The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

[00084] The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum,

calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, *N,N*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[00085] Also included in the compounds and compositions of the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of the present MK-2 inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

[00086] Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (Group IA) salts, alkaline earth metal (Group IIA) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trifluoroacetate, trimethylamine, diethylamine, *N,N*-dibenzylethylenediamine,

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chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N-methylglucamine*) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

[00087] The method of the present invention is useful for, but not limited to, the prevention and/or treatment of diseases and disorders that are mediated by TNFα and/or mediated by MK-2, including pain, inflammation and/or arthritis. For example, the compounds described herein would be useful for the treatment of any inflammation-related disorder described below, such as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. The compounds described herein would also be useful for the treatment of an inflammation-related disorder in a subject suffering from such an inflammation-associated disorder.

[00088] As used herein, the terms "treating", "treatment", "treated", or "to treat," mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis. The term "treatment" includes alleviation, elimination of causation of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described herein. The terms "prevent", "prevention", "prevented", or "to prevent," mean to prevent or to slow the appearance of symptoms associated with, but not limited to, any of the diseases or disorders described herein.

[00089] In preferred embodiments, the methods and compositions of the present invention encompass the prevention and/or treatment of pain, inflammation and inflammation-related disorders.

[00090] In other preferred embodiments, the methods and compositions of the present invention encompass the treatment of any one or more of the disorders selected from the group consisting of connective tissue and joint disorders, neoplasia disorders, cardiovascular disorders, otic disorders, ophthalmic disorders, respiratory disorders, gastrointestinal disorders, angiogenesis-related disorders, immunological disorders, allergic disorders, nutritional disorders, infectious diseases and disorders, endocrine disorders, metabolic disorders, neurological and

neurodegenerative disorders, psychiatric disorders, hepatic and biliary disorders, musculoskeletal disorders, genitourinary disorders, gynecologic and obstetric disorders, injury and trauma disorders, surgical disorders, dental and oral disorders, sexual dysfunction disorders, dermatologic disorders, hematological disorders, and poisoning disorders.

[00091] As used herein, the terms "neoplasia" and "neoplasia disorder", used interchangeably herein, refer to new cell growth that results from a loss of responsiveness to normal growth controls, *e.g.* to "neoplastic" cell growth. Neoplasia is also used interchangeably herein with the term "cancer" and for purposes of the present invention; cancer is one subtype of neoplasia. As used herein, the term "neoplasia disorder" also encompasses other cellular abnormalities, such as hyperplasia, metaplasia and dysplasia. The terms neoplasia, metaplasia, dysplasia and hyperplasia can be used interchangeably herein and refer generally to cells experiencing abnormal cell growth.

[00092] Both of the terms, "neoplasia" and "neoplasia disorder", refer to a "neoplasm" or tumor, which may be benign, premalignant, metastatic, or malignant. Also encompassed by the present invention are benign, premalignant, metastatic, or malignant neoplasias. Also encompassed by the present invention are benign, premalignant, metastatic, or malignant tumors. Thus, all of benign, premalignant, metastatic, or malignant neoplasia or tumors are encompassed by the present invention and may be referred to interchangeably, as neoplasia, neoplasms or neoplasia-related disorders. Tumors are generally known in the art to be a mass of neoplasia or "neoplastic" cells. Although, it is to be understood that even one neoplastic cell is considered, for purposes of the present invention to be a neoplasm or alternatively, neoplasia.

[00093] In still other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the connective tissue and joint disorders selected from the group consisting of arthritis, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, lumbar spondylarthrosis, carpal tunnel syndrome, canine

hip dysplasia, systemic lupus erythematosus, juvenile arthritis, osteoarthritis, tendonitis and bursitis.

[00094] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the neoplasia disorders selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, familial adenomatous polyposis, familial polyps, colon polyps, polyps, adenosarcoma, adenosquamous carcinoma, adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bile duct cancer, bladder cancer, brain stem glioma, brain tumors, breast cancer, bronchial gland carcinomas, capillary carcinoma, carcinoids, carcinoma, carcinosarcoma, cavernous, central nervous system lymphoma, cerebral astrocytoma, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, skin cancer, brain cancer, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epithelioid, esophageal cancer, Ewing's sarcoma, extragonadal germ cell tumor, fibrolamellar, focal nodular hyperplasia, gallbladder cancer, gastrinoma, germ cell tumors, gestational trophoblastic tumor, glioblastoma, glioma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, Hodgkin's lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, intraocular melanoma, invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, Kaposi's sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, lentigo maligna melanomas, leukemia-related disorders, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, malignant mesothelial tumors, malignant thymoma, medulloblastoma, medulloepithelioma, melanoma, meningeal, merkel cell

carcinoma, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, non-Hodgkin's lymphoma, oat cell carcinoma, oligodendroglial, oral cancer, oropharyngeal cancer, osteosarcoma, pancreatic polypeptide, ovarian cancer, ovarian germ cell tumor, pancreatic cancer, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, parathyroid cancer, penile cancer, pheochromocytoma, pineal and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm, pleuropulmonary blastoma, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, small intestine cancer, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, supratentorial primitive neuroectodermal tumors, thyroid cancer, undifferentiated carcinoma, urethral cancer, uterine sarcoma, uveal melanoma, verrucous carcinoma, vaginal cancer, vipoma, vulvar cancer, Waldenstrom's macroglobulinemia, well differentiated carcinoma, and Wilm's tumor.

[00095] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the cardiovascular disorders selected from the group consisting of myocardial ischemia, hypertension, hypotension, heart arrhythmias, pulmonary hypertension, hypokalemia, cardiac ischemia, myocardial infarction, cardiac remodeling, cardiac fibrosis, myocardial necrosis, aneurysm, arterial fibrosis, embolism, vascular plaque inflammation, vascular plaque rupture, bacterial-induced inflammation and viral induced inflammation, edema, swelling, fluid accumulation, cirrhosis of the liver, Bartter's syndrome, myocarditis, arteriosclerosis, atherosclerosis, calcification (such as vascular calcification and valvar calcification), coronary artery disease,

heart failure, congestive heart failure, shock, arrhythmia, left ventricular hypertrophy, angina, diabetic nephropathy, kidney failure, eye damage, vascular diseases, migraine headaches, aplastic anemia, cardiac damage, diabetic cardiac myopathy, renal insufficiency, renal injury, renal arteriopathy, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache.

[00096] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the metabolic disorders selected from the group consisting of obesity, overweight, type I and type II diabetes, hypothyroidism, and hyperthyroidism.

[00097] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the respiratory disorders selected from the group consisting of asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary edema, pulmonary embolism, pneumonia, pulmonary sarcoisosis, silicosis, pulmonary fibrosis, respiratory failure, acute respiratory distress syndrome and emphysema.

[00098] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the angiogenesis-related disorders selected from the group consisting of angiofibroma, neovascular glaucoma, arteriovenous malformations, arthritis, osler-weber syndrome, atherosclerotic plaques, psoriasis, corneal graft neovascularization, pyogenic granuloma, delayed wound healing, retrolental fibroplasias, diabetic retinopathy, scleroderma, granulations, solid tumors, hemangioma, trachoma, hemophilic joints, vascular adhesions, hypertrophic scars, age-related macular degeneration, coronary artery disease, stroke, cancer, AIDS complications, ulcers and infertility.

[00099] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the infectious diseases and disorders selected from the group consisting of

viral infections, bacterial infections, prion infections, spirochetes infections, mycobacterial infections, rickettsial infections, chlamydial infections, parasitic infections and fungal infections.

[000100] In still further embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the infectious diseases and disorders selected from the group consisting of hepatitis, HIV (AIDS), small pox, chicken pox, common cold, bacterial influenza, viral influenza, warts, oral herpes, genital herpes, herpes simplex infections, herpes zoster, bovine spongiform encephalopathy, septicemia, streptococcus infections, staphylococcus infections, anthrax, severe acquired respiratory syndrome (SARS), malaria, African sleeping sickness, yellow fever, chlamydia, botulism, canine heartworm, rocky mountain spotted fever, lyme disease, cholera, syphilis, gonorrhea, encephalitis, pneumonia, conjunctivitis, yeast infections, rabies, dengue fever, Ebola, measles, mumps, rubella, West Nile virus, meningitis, gastroenteritis, tuberculosis, hepatitis, and scarlet fever.

[000101] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the neurological and neurodegenerative disorders selected from the group consisting of headaches, migraine headaches, Alzheimer's disease, Parkinson's disease, dementia, memory loss, senility, amyotrophy, ALS, amnesia, seizures, multiple sclerosis, muscular dystrophies, epilepsy, schizophrenia, depression, anxiety, attention deficit disorder, hyperactivity, bulimia, anorexia nervosa, anxiety, autism, phobias, spongiform encephalopathies, Creutzfeldt-Jakob disease, Huntington's Chorea, ischemia, obsessive-compulsive disorder, manic depression, bipolar disorders, drug addiction, alcoholism and smoking addiction.

[000102] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the dermatological disorders selected from the group consisting of acne, psoriasis, eczema, burns, poison ivy, poison oak and dermatitis.

[000103] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the surgical disorders selected from the group consisting of pain and swelling following surgery, infection following surgery and inflammation following surgery.

[000104] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the gastrointestinal disorders selected from the group consisting of inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, gastritis, irritable bowel syndrome, diarrhea, constipation, dysentery, ulcerative colitis, gastric esophageal reflux, gastric ulcers, gastric varices, ulcers, and heartburn.

[000105] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the otic disorders selected from the group consisting of otic pain, inflammation, otorrhea, otalgia, fever, otic bleeding, Lermoyez's syndrome, Meniere's disease, vestibular neuronitis, benign paroxysmal positional vertigo, herpes zoster oticus, Ramsay Hunt's syndrome, viral neuronitis, ganglionitis, geniculate herpes, labyrinthitis, purulent labyrinthitis, viral endolymphatic labyrinthitis, perilymph fistulas, noise-induced hearing loss, presbycusis, drug-induced ototoxicity, acoustic neuromas, aerotitis media, infectious myringitis, bullous myringitis, otitis media, otitis media with effusion, acute otitis media, secretory otitis media, serous otitis media, acute mastoiditis, chronic otitis media, otitis externa, otosclerosis, squamous cell carcinoma, basal cell carcinoma, nonchromaffin paragangliomas, chemodectomas, globus jugulare tumors, globus tympanicum tumors, external otitis, perichondritis, aural eczematoid dermatitis, malignant external otitis, subperichondrial hematoma, ceruminomas, impacted cerumen, sebaceous cysts, osteomas, keloids, otalgia, tinnitus, vertigo, tympanic membrane infection, typanitis, otic furuncles, otorrhea, acute mastoiditis, petrositis, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis,

subdural empyema, otitic hydrocephalus, Dandy's syndrome, bullous myringitis, cerumen-impacted, diffuse external otitis, foreign bodies, keratosis obturans, otic neoplasm, otomycosis, trauma, acute barotitis media, acute eustachian tube obstruction, post-otic surgery, postsurgical otalgia, cholesteatoma, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis, subdural empyema and otitic hydrocephalus.

[000106] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the ophthalmic disorders selected from the group consisting of retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue, conjunctivitis, age-related macular degeneration diabetic retinopathy, detached retina, glaucoma, vitelliform macular dystrophy type 2, gyrate atrophy of the choroid and retina, conjunctivitis, corneal infection, fuchs' dystrophy, iridocorneal endothelial syndrome, keratoconus, lattice dystrophy, map-dot-fingerprint dystrophy, ocular herpes, pterygium, myopia, hyperopia, and cataracts.

[000107] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of menstrual cramps, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, closed head injury, liver disease, and endometriosis.

[000108] As used herein, the terms "TNFα mediated disease or disorder" are meant to include, without limitation, each of the symptoms or diseases that are mentioned above.

[000109] The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of or treatment of any one of the TNFα mediated diseases or disorders. The subject is typically a mammal. "Mammal", as that term is used herein, refers to any

animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc., Preferably, the mammal is a human.

[000110] For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of prevention and/or treatment of a TNFα mediated diseases or disorders. The subject may be a human subject who is at risk of obtaining a TNFα mediated disease or disorder, such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-causing agents, exposure to pathogenic agents and the like.

[000111] The subject pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[000112] In particular, the pharmaceutical compositions of the present invention can be administered orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic

acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[000113] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[000114] Aqueous suspensions can be produced that contain the MK-2 inhibitors in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000115] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[000116] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[000117] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[000118] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[000119] Syrups and elixirs containing the novel MK-2 inhibitory compounds may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[000120] The subject compositions can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or oleagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending

medium. For this purpose, any bland fixed oil may be employed including synthetic mono-, or di-, glycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

[000121] The subject compositions can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

[000122] The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

[000123] Various delivery systems include capsules, tablets, and gelatin capsules, for example.

[000124] The following examples describe preferred embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples all percentages are given on a weight basis unless otherwise indicated.

GENERAL INFORMATION FOR PREPARATION METHODS:

[000125] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

[000126] NMR analysis:

[000127] Proton nuclear magnetic resonance spectra were obtained on a Varian Unity Innova 400, a Varian Unity Innova 300 a Varian Unity 300, a Bruker AMX 500 or a Bruker AV-300 spectrometer. Chemical shifts are given in ppm (δ) and coupling constants, J, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric

pressure Ionization (APCI) mass spectrometer, a Finnigan LCQ Duo LCMS Ion trap electrospray ionization (ESI) mass spectrometer, a PerSeptive Biosystems Mariner TOF HPLC-MS (ESI), or a Waters ZQ mass spectrometer (ESI).

[000128] Determination of MK-2 IC_{50}:

[000129] Recombinant MAPKAPK2 was phosphorylated at a concentration of 42-78 μM by incubation with 0.23 μM of active p38α in 50 mM HEPES, 0.1 mM EDTA, 10 mM magnesium acetate, and 0.25 mM ATP, pH 7.5 for one hour at 30°C.

[000130] The phosphorylation of HSP-peptide (KKKALSRQLSVAA) by MAPKAPK2 was measured using an anion exchange resin capture assay method. The reaction was carried out in 50 mM β-glycerolphosphate, 0.04 % BSA, 10 mM magnesium acetate, 2% DMSO and 0.8 mM dithiotheritol, pH 7.5 in the presence of the HSP-peptide with 0.2 μCi [γ^{33}P]ATP and 0.03mM ATP. The reaction was initiated by the addition of 15 nM MAPKAPK2 and was allowed to incubate at 30°C for 30 min. The reaction was terminated and [γ^{33}P]ATP was removed from solution by the addition of 150 μl of AG 1X8 ion exchange resin in 900 mM sodium formate pH 3.0. A 50 μl aliquot of head volume was removed from the quenched reaction mixture and added to a 96-well plate, 150 μl of Microscint-40 (Packard) was added and the amount of phosphorylated-peptide was determined. Allow the Microscint to sit in the plates for 60 minutes prior to counting.

[000131] Compounds are evaluated as potential inhibitors of the MK2 kinase by measuring their effects on MK2 phosphorylation of the peptide substrate. Compounds may be screened initially at two concentrations prior to determination of IC_{50} values. Screening results are expressed as percent inhibition at the concentrations of compound tested. For IC_{50} value determinations, compounds are tested at six concentrations in ten-fold serial dilutions with each concentration tested in triplicate. Results are expressed as IC_{50} values in micromolar. The assay is performed at a final concentration of 2% DMSO.

[000132] U937 Cell TNFα release assay

[000133] The human monocyte-like cell line, U937 (ATCC #CRL-1593.2), is cultured in RPMI1640 media with 10% heat-inactivated fetal calf serum (GIBCO), glutamine and pen/strep at 37°C and 5% CO_2. Differentiation of U937 to monocytic/macrophage-like cells is induced by the addition of phorbol12-myristate 13-acetate (Sigma) at final concentration of 20 ng/ml to a culture of U937 cells at ~0.5 million cells/ml and incubated for 24 hrs. The cells are centrifuged, washed with PBS and resuspended in fresh media without PMA and incubated for 24 hrs. Cells adherent to the culture flask are harvested by scraping, centrifugation, and resuspended in fresh media to 2 million cells/ml, and 0.2 ml is aliquoted to each of 96 wells in flat-bottom plate. Cells are then incubated for an additional 24 hrs to allow for recovery. The media is removed from the cells, and 0.1 ml of fresh media is added per well. 0.05 ml of serially diluted compound or control vehicle (Media with DMSO) is added to the cells. The final DMSO concentration does not exceed 1%. After 1hr incubation, 0.05 ml of 400ng/ml LPS (E Coli serotype 0111:B4, Sigma) in media is added for final concentration of 100 ng/ml. Cells are incubated at 37°C for 4 hrs. After 4hrs incubation, supernatants are harvest and assayed by ELISA for the presence of TNFα.

[000134] U937 cell TNFα ELISA

[000135] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with purified mouse monoclonal IgG1 anti-human TNFα antibody (R&D Systems #MAB610; 1.25 ug/ml in sodium bicarbonate pH 8.0, 0.1 ml/well) and incubated at 4°C. Coating solution was aspirated the following day and wells were blocked with 1 mg/ml gelatin in PBS (plus 1x thimerasol) for 2 days at 4°C. Prior to using, wells were washed 3x with wash buffer (PBS with 0.05% Tween). Cultured media samples were diluted in EIA buffer (5 mg/ml bovine γ-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS), added to wells (0.1 ml/well) in triplicate and allowed to incubate for 1.5 hr at 37°C in a humidified

chamber. Plates were again washed and 0.1 ml/well of a mixture of rabbit anti-human TNFα polyclonal antibodies in EIA buffer (1:400 dilution of Sigma #T8300, and 1:400 dilution of Calbiochem #654250) was added for 1 hr at 37°C. Plates were washed as before and peroxidase-conjugated goat anti-rabbit IgG (H+L) antibody (Jackson ImmunoResearch #111-035-144, 1 ug/ml in EIA buffer, 0.1 ml/well) was added for 45 min. After final washing, plates were developed with peroxidase-ABTS solution (Kirkegaard/Perry #50-66-01, 0.1 ml/well). Enzymatic conversion of ABTS to colored product was measured after 5-30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices) at 405 nm. TNF levels were quantitated from a recombinant human TNFα (R&D Systems #210-TA-010) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. IC_{50} values for compounds were generated using BioAssay Solver.

[000136] Lipopolysaccharide (LPS)-Induced TNFα Production.

[000137] Adult male 225-250 gram Lewis rats (Harlan Sprague-Dawley) were used. Rats were fasted 18 hr prior to oral dosing, and allowed free access to water throughout the experiment. Each treatment group consisted of 5 animals.

[000138] Compounds were prepared as a suspension in a vehicle consisting of 0.5% methylcellulose, 0.025% Tween-20 in PBS. Compounds or vehicle were orally administered in a volume of 1 ml using an 18 gauge gavage needle. LPS (E. coli serotype 0111:B4, Lot #39H4103, Cat. # L-2630, Sigma) was administered 1-4 hr later by injection into the penile vein at a dose of 1 mg/kg in 0.5 ml sterile saline. Blood was collected in serum separator tubes via cardiac puncture 1.5 hr after LPS injection, a time point corresponding to maximal TNFα production. After clotting, serum was withdrawn and stored at -20°C until assay by ELISA (described below).

[000139] Rat LPS TNFα ELISA

[000140] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with 0.1 ml per well of a Protein G purified fraction of a 2.5 ug/ml of hamster anti-mouse/rat TNFα monoclonal antibody TN19.12 (2.5 ug/ml in PBS, 0.1 ml/well). The hybridoma cell line was kindly provided by Dr. Robert Schreiber, Washington University. Wells were blocked the following day with 1 mg/ml gelatin in PBS. Serum samples were diluted in a buffer consisting of 5 mg/ml bovine γ-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS, and 0.1 ml of diluted serum was added wells in duplicate and allowed to incubate for 2 hr at 37°C. Plates were washed with PBS-Tween, and 0.1 ml per well of a 1:300 dilution of rabbit anti-mouse/rat TNFα antibody (BioSource International, Cat. #AMC3012) was added for 1.5 hr at 37°C. Plates were washed, and a 1:1000 fold dilution of peroxidase-conjugated donkey anti-rabbit IgG antibody (Jackson ImmunoResearch, Cat. #711-035-152) was added for 45 min. After washing, plates were developed with 0.1 ml of ABTS-peroxide solution (Kirkegaard/Perry, Cat. #50-66-01). Enzymatic conversion of ABTS to colored product was measured after ~30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices Corp.) at 405 nm. TNF levels in serum were quantitated from a recombinant rat TNFα (BioSource International, Cat. #PRC3014) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. Results are expressed in percent inhibition of the production of TNFα as compared to blood collected from control animals dosed only with vehicle.

[000141] NMR analysis:

[000142] Proton nuclear magnetic resonance spectra were obtained on a Varian Unity Innova 400, a Varian Unity Innova 300 a Varian Unity 300, a Bruker AMX 500 or a Bruker AV-300 spectrometer. Chemical shifts are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra and

the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric pressure ionization (APCI) mass spectrometer, a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer, a PerSeptive Biosystems Mariner TOF HPLC-MS (ESI), or a Waters ZQ mass spectrometer (ESI).

[000143] Determination of MK-2 IC_{50}:

[000144] Recombinant MAPKAPK2 was phosphorylated at a concentration of 42-78 μM by incubation with 0.23 μM of active p38α in 50 mM HEPES, 0.1 mM EDTA, 10 mM magnesium acetate, and 0.25 mM ATP, pH 7.5 for one hour at 30°C.

[000145] The phosphorylation of HSP-peptide (KKKALSRQLSVAA) by MAPKAPK2 was measured using an anion exchange resin capture assay method. The reaction was carried out in 50 mM β-glycerolphosphate, 0.04 % BSA, 10 mM magnesium acetate, 2% DMSO and 0.8 mM dithiothreitol, pH 7.5 in the presence of the HSP-peptide with 0.2 μCi [γ^{33}P]ATP and 0.03mM ATP. The reaction was initiated by the addition of 15 nM MAPKAPK2 and was allowed to incubate at 30°C for 30 min. The reaction was terminated and [γ^{33}P]ATP was removed from solution by the addition of 150 μl of AG 1X8 ion exchange resin in 900 mM sodium formate pH 3.0. A 50 μl aliquot of head volume was removed from the quenched reaction mixture and added to a 96-well plate, 150 μl of Microscint-40 (Packard) was added and the amount of phosphorylated-peptide was determined. Allow the Microscint to sit in the plates for 60 minutes prior to counting.

[000146] Compounds are evaluated as potential inhibitors of the MK-2 kinase by measuring their effects on MK-2 phosphorylation of the peptide substrate. Compounds may be screened initially at two concentrations prior to determination of IC_{50} values. Screening results are expressed as percent inhibition at the concentrations of compound tested. For IC_{50} value determinations, compounds are tested at six concentrations in ten-fold serial dilutions with each concentration tested in triplicate. Results are

expressed as IC_{50} values in micromolar. The assay is performed at a final concentration of 2% DMSO.

[000147] U937 Cell TNFα release assay

[000148] The human monocyte-like cell line, U937 (ATCC #CRL-1593.2), is cultured in RPMI1640 media with 10% heat-inactivated fetal calf serum (GIBCO), glutamine and pen/strep at 37°C and 5% CO_2. Differentiation of U937 to monocytic/macrophage-like cells is induced by the addition of phorbol12-myristate 13-acetate (Sigma) at final concentration of 20 ng/ml to a culture of U937 cells at ~0.5 million cells/ml and incubated for 24 hrs. The cells are centrifuged, washed with PBS and resuspended in fresh media without PMA and incubated for 24 hrs. Cells adherent to the culture flask are harvested by scraping, centrifugation, and resuspended in fresh media to 2 million cells/ml, and 0.2 ml is aliquoted to each of 96 wells in flat-bottom plate. Cells are then incubated for an additional 24 hrs to allow for recovery. The media is removed from the cells, and 0.1 ml of fresh media is added per well. 0.05 ml of serially diluted compound or control vehicle (Media with DMSO) is added to the cells. The final DMSO concentration does not exceed 1%. After 1hr incubation, 0.05 ml of 400ng/ml LPS (E Coli serotype 0111:B4, Sigma) in media is added for final concentration of 100 ng/ml. Cells are incubated at 37°C for 4 hrs. After 4hrs incubation, supernatants are harvest and assayed by ELISA for the presence of TNFα.

[000149] U937 cell TNFα ELISA

[000150] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with purified mouse monoclonal IgG1 anti-human TNFα antibody (R&D Systems #MAB610; 1.25 µg/ml in sodium bicarbonate pH 8.0, 0.1 ml/well) and incubated at 4°C. Coating solution was aspirated the following day and wells were blocked with 1 mg/ml gelatin in PBS (plus 1x thimerasol) for 2 days at 4°C. Prior to using, wells were washed 3x with wash buffer (PBS with 0.05% Tween). Cultured media samples were diluted in EIA buffer (5 mg/ml bovine gamma-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS), added to wells (0.1 ml/well) in

triplicate and allowed to incubate for 1.5 hr at 37°C in a humidified chamber. Plates were again washed and 0.1 ml/well of a mixture of rabbit anti-human TNFα polyclonal antibodies in EIA buffer (1:400 dilution of Sigma #T8300, and 1:400 dilution of Calbiochem #654250) was added for 1 hr at 37°C. Plates were washed as before and peroxidase-conjugated goat anti-rabbit IgG (H+L) antibody (Jackson ImmunoResearch #111-035-144, 1 ug/ml in EIA buffer, 0.1 ml/well) was added for 45 min. After final washing, plates were developed with peroxidase-ABTS solution (Kirkegaard/Perry #50-66-01, 0.1 ml/well). Enzymatic conversion of ABTS to colored product was measured after 5-30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices) at 405 nm. TNF levels were quantitated from a recombinant human TNFα (R&D Systems #210-TA-010) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. IC_{50} values for compounds were generated using BioAssay Solver.

[000151] Lipopolysaccharide (LPS)-Induced TNFα Production.

[000152] Adult male 225-250 gram Lewis rats (Harlan Sprague-Dawley) were used. Rats were fasted 18 hr prior to oral dosing, and allowed free access to water throughout the experiment. Each treatment group consisted of 5 animals.

[000153] Compounds were prepared as a suspension in a vehicle consisting of 0.5% methylcellulose, 0.025% Tween-20 in PBS. Compounds or vehicle were orally administered in a volume of 1 ml using an 18 gauge gavage needle. LPS (E. coli serotype 0111:B4, Lot #39H4103, Cat. # L-2630, Sigma) was administered 1-4 hr later by injection into the penile vein at a dose of 1 mg/kg in 0.5 ml sterile saline. Blood was collected in serum separator tubes via cardiac puncture 1.5 hr after LPS injection, a time point corresponding to maximal TNFα production. After clotting, serum was withdrawn and stored at -20°C until assay by ELISA (described below).

[000154] Rat LPS TNFα ELISA

[000155] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with 0.1 ml per well of a Protein G purified fraction of a 2.5 ug/ml of hamster anti-mouse/rat TNFα monoclonal antibody TN19.12 (2.5 ug/ml in PBS, 0.1 ml/well). The hybridoma cell line was provided by Dr. Robert Schreiber, Washington University. Wells were blocked the following day with 1 mg/ml gelatin in PBS. Serum samples were diluted in a buffer consisting of 5 mg/ml bovine gamma-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS, and 0.1 ml of diluted serum was added wells in duplicate and allowed to incubate for 2 hr at 37°C. Plates were washed with PBS-Tween, and 0.1 ml per well of a 1:300 dilution of rabbit anti-mouse/rat TNFα antibody (BioSource International, Cat. #AMC3012) was added for 1.5 hr at 37°C. Plates were washed, and a 1:1000 fold dilution of peroxidase-conjugated donkey anti-rabbit IgG antibody (Jackson ImmunoResearch, Cat. #711-035-152) was added for 45 min. After washing, plates were developed with 0.1 ml of ABTS-peroxide solution (Kirkegaard/Perry, Cat. #50-66-01). Enzymatic conversion of ABTS to colored product was measured after ~30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices Corp.) at 405 nm. TNF levels in serum were quantitated from a recombinant rat TNFα (BioSource International, Cat. #PRC3014.) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. Results are expressed in percent inhibition of the production of TNFα as compared to blood collected from control animals dosed only with vehicle.

[000156] Synthesis of MK-2 inhibiting compounds of the present invention:

[000157] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra were obtained on a Varian-300, Bruker AMX 500 or a Bruker AV-300 spectrometer. Spectra are given in ppm (δ) and coupling constants, *J*,

are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra. 3-Bromobenzotrifluoride was used as an internal standard in ^{19}F nuclear magnetic resonance spectra to calibrate the amount of TFA for TFA salts. Mass spectra were obtained on a Mariner electrospray ionization (ESI), Perkin Elmer Sciex 100 atmospheric pressure ionization (APCI) mass spectrometer, Hewlett Packard G1947A LCMS ion trap ionization (ESI), or a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer. Thin-layer chromatography (TLC) was performed using Analtech silica gel plates and visualized by ultraviolet (UV) light. HPLC analyses were obtained using a YMC CombiScreen ODS-A (50 x 4.6 mm) with UV with diode array detection, using aqueous TFA in acetonitrile as the eluent on a Hewlett Packard 1100, or a Phenomenex C18 Luna column (150 x 4.6 mm) with UV detection at 254 nm, using aqueous TFA in acetonitrile as the eluent on a Varian Prostar. Purification using preparative HPLC was performed using a Phenomenex C18 Luna column (250 x 22 mm) with UV detection at 254 nm, using aqueous TFA in acetonitrile as the eluent on a Varian Prostar, or using a Waters Deltapack C 18 column (47 x 300 mm) with UV detection at 254 nm, using aqueous TFA in acetonitrile as the eluent on a Gilson. All reactions were carried out under nitrogen unless specified.

EXAMPLE 1

[000158] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride.

[000159] Step 1. The preparation of lithium (1Z)-4-ethoxy-3,4-dioxo-1-pyridin-4-ylbut-1-en-1-olate.

[000160] 4-Acetylpyridine (960.4 g, 7.93 mole) and diethyl oxylate (1170.8 g, 8.08 mole) were dissolved in 8 L toluene in a 22 L reactor. The reaction was cooled to –78 °C under N_2, and a 1 M solution of Lithium bis(trimetnylsilyl)amide in THF (8.08 L, 8.08 mole) was added in a medium stream over 45 minutes, keeping the temperature near 10°C. When the addition was complete, the reaction was allowed to warm to

room temperature with stirring for 18 hours. The reaction mixture was filtered, and the solid washed with toluene followed by diethyl ether. The product was air dried and desiccated to afford 1562.5 g of the lithium salt of the diketoester (87% yield).

[000161] Step 2. Lithium (1Z)-4-ethoxy-3,4-dioxo-1-pyridin-4-ylbut-1-en-1-olate (1562.5 g, 6.88 mole) was placed in a 22 L reactor and slurried in 7 L of ethanol. The slurry was heated to 63°C under N_2 with mixing. The heating mantle was removed, and the temperature stabilized at about 63°C. To this mixture hydrazine monohydrochloride (476.3 g, 6.95) was added. After a few minutes a slow exotherm started. An ice/water bath was applied when the reaction reached 80°C. The ice bath was removed, and the temperature held steady at 80°C. The heating mantle was re-installed, and the reaction was maintained at 80.5°C (reflux) for one hour. The reaction was cooled and stirred at room temperature for 18 hours. The mixture was filtered, and the solids washed with ethanol followed by diethyl ether. The product was air dried and desiccated to afford 1365.6 g (91% yield) of the desired pyrazole as a tan solid. LCMS showed a single peak with m/z 218 (M+H). ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.61 (d, 2H), 7.83 (d, 2H), 7.44 (s, 1H), 4.31 (q, 2H), 1.30 (t, 3H).

[000162] Step 3. To a cooled (0°C) solution of ethyl 3-pyridin-4-yl-1H-pyrazole-5-carboxylate (5.57 g, 25.6 mmol) in anhydrous DMF (140 mL) was added lithium *t*-butoxide (1M in THF, 38.5 mL) dropwise. The reaction stirred for 30 min, then a solution of *tert*-butyl 2-bromoethylcarbamate (8.62 g, 38.5 mmol) and sodium iodide (5.77 g, 38.5 mmol) in anhydrous DMF (25 mL) was added dropwise. The reaction was allowed to stir and warm to room temperature for 20 h. The reaction was poured into water and brine, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated to an orange solid. The solid was rinsed with diethyl ether to afford an off-white solid (5.49 g, 59.5% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.59 (d, 2H), 7.82 (d, 2H), 7.51 (s, 1H), 6.90 (t, 1H), 4.58 (t, 2H), 4.33 (q, 2H), 3.38-3.33 (m, 2H), 1.34 (t, 3H), 1.27 (s, 9H); HRMS calculated for (M + H) 361.1870, found 361.1890.

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EXAMPLE 2

[000163] This example illustrates the production of ethyl 1-(2-amino-ethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride.

[000164] To a flask charged with ethyl 1-{2-[(tert-butoxycarbonyl)amino] ethyl}-3-pyridin-4-yl-1H-pyrazole-5-carboxylate (5.39 g, 15.0 mmol) was added 4N HCl/dioxane (20 mL). After 1 h the reaction mixture was filtered and rinsed with diethyl ether to afford an off-white solid (5.02 g, 100% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.93 (d, 2H), 8.48-8.43 (m, 5H), 7.95 (s, 1H), 4.89 (t, 2H), 4.37 (q, 2H), 3.41-.3.38 (m, 2H), 1.35 (t, 3H); HRMS calculated for (M + H) 261.1346, found 261.1317.

EXAMPLE 3

[000165] This example illustrates the production of 2-pyridin-4-yl-6,7-dihydro-pyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000166] A flask was charged with ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride (1.13 g, 3.39 mmol), NH_4OH (30 mL), and ethanol (15 mL). After stirring for 1 h, the reaction mixture was purified by Gilson RP HPLC (5-95% acetonitrile/water). The appropriate fractions were concentrated to a pale yellow solid (0.725 g, 65.4% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.81 (d, 2H), 8.40 (br s, 1H), 8.22 (d, 2H), 7.67 (s, 1H), 4.43 (t, 2H), 3.70-3.64 (m, 2H); HRMS calculated for (M + H) 215.0927, found 215.0885.

EXAMPLE 4

[000167] This example illustrates the production of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000168] A solution of ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride (0.794 g, 2.38 mmol) and $LiOH•H_2O$ (0.310 g, 7.40 mmol) in 30 mL of THF/H_2O (1:1) was heated to 80°C with stirring. After 2 h the reaction mixture was purified by Gilson RP HPLC (5-95% acetonitrile/water). The appropriate fractions were concentrated to a white solid (0.442 g, 53.7% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.96 (br s,

2H), 8.48 (br s, 2H), 8.07-7.91 (m, 4H), 4.87 (br s, 2H), 3.41 (br s, 2H); HRMS calculated for (M + H) 233.1033, found 233.1025.

EXAMPLE 5

[000169] This example illustrates the production of 1-(2-{[3-(5-methyl-2-furyl)butyl]amino}ethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000170] Ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride (0.806 g, 2.42 mmol) was neutralized by stirring with morpholino-methylpolystyrene resin (4.15 g, ~3.5 mmol base/g resin) in dichloromethane/methanol (20:1) for 1 h. The resin was filtered, rinsed with methanol, and the filtrates concentrated. The resulting white residue was dissolved in dichloromethane/methanol (20:1). Six drops of glacial acetic acid were added with stirring, followed by 3-(5-methyl-2-furyl)butyraldehyde (0.422 g, 6.60 mmol. After 5 min, sodium triacetoxyborohydride (1.04 g, 4.90 mmol) was added. The reaction stirred for 1 h, both the mono- and dialkylated products formed. The reaction was quenched with water and extracted with dichloromethane. The organic layers were concentrated to an oil, which was subjected to hydrolysis conditions [3 eq $LiOH \cdot H_2O$, THF/H_2O (1:1)] for 3 h. The resulting product mixture was purified by Gilson RP HPLC (5-95% acetonitrile/water) and the fractions corresponding to the monoalkylated product were concentrated to a mauve solid (0.106 g, 9.0% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.77-8.75 (m, 4H), 8.08 (d, 2H), 7.72 (s, 1H), 5.97-5.93 (m, 2H), 4.87 (t, 2H), 3.51-3.47 (m, 2H), 2.96 (br s, 2H), 2.82 (q, 1H), 2.19 (s, 3H), 1.92-1.72 (m, 2H), 1.16 (d, 3H); HRMS calculated for (M + H) 233.1033, found 233.1025.

EXAMPLE 6

[000171] This example illustrates the production of ethyl 3-(1-oxidopyridin-4-yl)-1H-pyrazole-5-carboxylate.

[000172] A flask was charged with ethyl 3-pyridin-4-yl-1H-pyrazole-5-carboxylate (5.04 g, 23.2 mmol) and 3-chloroperoxybenzoic acid (7.06g, 27.8 mmol) in 70 mL of dichloromethane. After 2 h the reaction was

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concentrated *in vacuo* to remove most of the dichloromethane. To the residue was added 5% ethyl acetate/hexanes and the suspension filtered. The solid was slurried in $NaHCO_3$ (sat.), filtered, and rinsed with $NaHCO_3$ (sat.). The solid was then slurried in NaS_2O_3, filtered, and then rinsed with water. The solid was slurried up in ethanol and concentrated to afford an orange-tan solid (4.25 g, 78.0% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.24 (d, 2H), 7.86 (d, 2H), 7.42 (s, 1H), 4.31 (q, 2H), 1.31 (t, 3H); HRMS calculated for (M + H) 234.0873, found 234.0877.

EXAMPLE 7

[000173] This example illustrates the production of ethyl 3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate.

[000174] A suspension of ethyl 3-(1-oxidopyridin-4-yl)-1H-pyrazole-5-carboxylate (11.16 g, 14.9 mmol) and phosphorus oxychloride (110 mL, 1.2 mol) was heated to 106°C for 48 h. The reaction mixture was concentrated, and then dissolved in chloroform (300 mL) and ice water (300 mL). Solid $NaHCO_3$ was added until foaming was no longer observed, then the heterogeneous solution was extracted multiple times with chloroform. The organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was triturated with dichloromethane. The solid was filtered and rinsed with ethyl acetate, and then with diethyl ether to afford a pale yellow solid (3.59 g, 29.8% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 14.41 (br s, 1H), 8.44 (d, 1H), 7.98 (s, 1H), 7.88 (d, 1H), 7.61 (s, 1H), 4.33 (q, 2H), 1.32 (t, 3H); HRMS calculated for (M + H) 252.0534, found 252.0508.

EXAMPLE 8

[000175] This example illustrates the production of ethyl 1-{3-[(tert-butoxycarbonyl)- amino]propyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate.

[000176] Synthesis conducted as in the preparation of ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-pyridin-4-yl-1H-pyrazole-5-carboxylate using ethyl 3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (3.36 g, 13.3 mmol), lithium *t*-butoxide (1M in THF, 17.0 mL), *tert*-butyl 3-

bromopropylcarbamate (3.81 g, 16.0 mmol) and sodium iodide (2.39 g, 16.0 mmol). Chromatographic purification (25% ethyl acetate/hexane) afforded a white solid (3.29 g, 60.5% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.42 (d, 1H), 7.95 (s, 1H), 7.86 (dd, 1H), 7.67 (s, 1H), 6.85 (dd, 1H), 4.54 (t, 2H), 4.35 (q, 2H), 2.98-2.92 (m, 2H), 1.98-1.88 (m, 2H), 1.36-1.31 (m, 12H); HRMS calculated for (M + H) 409.1637, found 409.1634.

EXAMPLE 9

[000177] This example illustrates the production ofethyl 1-{2-[(tert-butoxycarbonyl)-amino]ethyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate.

[000178] Synthesis was conducted as in the preparation of ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-pyridin-4-yl-1H-pyrazole-5-carboxylate, using ethyl 3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (6.00 g, 23.8 mmol), lithium *t*-butoxide (1M in THF, 31.0 mL), *tert*-butyl 2-bromoethylcarbamate (6.59 g, 29.4 mmol), and sodium iodide (4.41 g, 29.4 mmol). Flash chromatography (25% ethyl acetate/hexane) afforded a white solid (6.07 g, 64.6% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.43 (d, 1H), 7.94 (s, 1H), 7.85 (dd, 1H), 7.66 (s, 1H), 6.89 (t, 1H), 4.59 (t, 2H), 4.33 (q, 2H), 3.39-3.32 (m, 2H), 1.36-1.23 (m, 12H); HRMS calculated for (M + H) 395.1481, found 395.1512.

EXAMPLE 10

[000179] This example illustrates the production of2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000180] A flask was charged with ethyl 1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (6.50 g, 15.9 mmol) and 4N HCl/dioxane (45 mL). The reaction mixture stirred for 1 h, then the suspension was filtered and the solid rinsed with diethyl ether. This solid was taken up in ethanol (20 mL) and NH_4OH (40 mL). After stirring for 20 h, the suspension was filtered and rinsed with ethanol and diethyl ether to afford a white solid (3.64 g, 87.4% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.41 (d, 1H), 8.35 (t, 1H), 7.90 (s, 1H), 7.83 (d, 1H), 7.48

(s, 1H), 4.49 (t, 2H), 3.24-3.18 (m, 2H), 2.20-2.14 (m, 2H), HRMS calculated for (M + H) 263.0694, found 263.0689.

EXAMPLE 11

[000181] This example illustrates the production of ethyl 1-[3-[(tert-butoxycarbonyl) amino]propyl]-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate.

[000182] A flask was charged with ethyl 1-[3-[(tert-butoxycarbonyl)amino] propyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.875 g, 2.14 mmol), 3-nitrophenylboronic acid (0.536 g, 3.21 mmol), 2M Na_2CO_3 (9 mL), toluene (25 mL), and [1, 1' bis(diphenylphosphino) ferrocene]dichloropalladium(II), 1:1 complex with dichloromethane [Pd[dppf]Cl_2·CH_2Cl_2 (0.140 g, 0.170 mmol)], then purged with N_2 and heated at 90°C for 20 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Chromatographic purification (30% ethyl acetate/hexane) afforded a white solid (0.767 g, 72.4% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.75 (d, 1H), 8.68 (d, 1H), 8.54 (s, 1H), 8.30 (m, 1H), 7.91 (dd, 1H), 7.84-7.70 (m, 2H), 6.87 (dd, 1H), 4.58 (t, 2H), 4.36 (q, 2H), 3.00-2.95 (m, 2H), 1.98-1.92 (m, 2H), 1.38-1.31 (m, 12H); HRMS calculated for (M + H) 496.2191, found 496.2175.

EXAMPLE 12

[000183] This example illustrates the production of 1-(3-aminopropyl)-3-[2-(3 nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxamide trifluoroacetate.

[000184] Ammonia gas was bubbled into a pressure tube charged with ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate (0.084 g, 0.17 mmol) in 10 mL ethanol and cooled to –78 °C. The tube was then sealed and heated to 70°C for 6 days. The reaction mixture was concentrate *in vacuo*. To this residue was added 4N HCl/ dioxane (6 mL). After 1.5 h the solution was purified by Gilson RP HPLC (5-95% acetonitrile/water). The appropriate fractions were concentrated to a light tan solid (0.048 g, 60% yield): ^{1}H NMR

(DMSO-d_6 / 300 MHz) δ 8.94 (dd, 1H), 8.81 (d, 1H), 8.60 (d, 1H), 8.43 (s, 1H), 8.36 (dd, 1H), 8.20-8.09 (m, 4H), 7.87-7.74 (m, 3H), 4.66 (t, 2H), 2.86-2.79 (m, 2H), 2.20-2.15 (m, 2H); HRMS calculated for (M + H) 367.1513, found 367.1529.

EXAMPLE 13

[000185] This example illustrates the production of 1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxamide dihydrochloride.

[000186] Synthesis was conducted as for the production of 1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxamide trifluoroacetate using ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate (0.127 g, 0.254 mmol). The TFA salt residue was taken up in methanol and 4N HCl/dioxane. After 20 h the suspension was concentrated to an off-white solid (0.069 g, 0.16 mmol): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.90 (d, 1H), 9.78 (s, 1H), 8.87 (d, 1H), 8.69 (s, 1H), 8.46-8.39 (m, 2H), 8.22-8.08 (m, 5H), 7.96-7.89 (m, 2H), 7.82-7.78 (m, 2H), 4.67 (t, 2H), 2.86-2.77 (m, 2H), 2.25-2.16 (m, 2H); HRMS calculated for (M + H) 373.1771, found 373.1769.

EXAMPLE 14

[000187] This example illustrates the production of ethyl 1-[2-[(tertbutoxy-carbonyl)amino]ethyl]-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate.

[000188] Synthesis was conducted as in the preparation of ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate using ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.732 g, 1.85 mmol), 3-quinolinylboronic acid (0.481 g, 2.78 mmol), 2M Na_2CO_3 (7 mL), toluene (20 mL), and Pd[dppf]Cl_2·CH_2Cl_2 (0.121 g, 0.148 mmol). The black residue obtained from the aqueous work-up was triturated with dichloromethane to afford an off-white solid (0.615 g, 68.2% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.72 (s, 1H), 9.14 (s, 1H), 8.78 (d, 1H), 8.62 (s, 1H), 8.15-8.08 (m,

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2H), 7.90-7.82 (m, 3H), 7.71-7.66 (m, 1H), 6.94 (t, 1H), 4.64 (t, 2H), 4.37 (q, 2H), 3.39-3.32 (m, 2H), 1.39-1.28 (m, 12H); HRMS calculated for (M + H) 488.2292, found 488.2296.

EXAMPLE 15

[000189] This example illustrates the production of 2-[2-[4-(trifluoromethoxy)-phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000190] Synthesis was conducted as in the preparation of ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate using ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.954 g, 2.33 mmol), 3-quinolinylboronic acid (0.520 g, 3.00 mmol), 2M Na_2CO_3 (10 mL), toluene (25 mL), and $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.152 g, 0.186 mmol). Flash chromatography (25% ethyl acetate/hexane) afforded a beige solid (0.593g, 50.7% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.72 (d, 1H), 9.14 (d, 1H), 8.77 (d, 1H), 8.63 (s, 1H), 8.15-8.07 (m, 2H), 7.85-7.82 (m, 3H), 7.69 (dd, 1H), 6.88 (t, 1H), 4.60 (t, 2H), 4.37 (q, 2H), 3.02-2.96 (m, 2H), 2.01-1.93 (m, 2H), 1.39-1.34 (m, 12H); HRMS calculated for (M + H) 502.2449, found 502.2419.

EXAMPLE 16

[000191] This example illustrates the production of ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-[2-[4-(hydroxymethyl) phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate.

[000192] Synthesis was conducted as in the preparation of ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate using ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (1.100 g, 2.79 mmol), 4-hydroxymethyl-phenylboronic acid (0.550 g, 3.62 mmol), 2M Na_2CO_3 (12 mL), toluene (32 mL), and $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.182 g, 0.223 mmol). The black residue obtained from the aqueous work-up was triturated with dichloromethane to yield an off-white solid (0.567 g, 43.6% yield): ^1H NMR

(DMSO-d_6 / 300 MHz) δ 8.67 (d, 1H), 8.32 (s, 1H), 8.15 (d, 2H), 7.78-7.76 (m, 2H), 7.45 (d, 2H), 6.92 (t, 1H), 5.26 (t, 1H), 4.62-4.58 (m, 4H), 4.35 (q, 2H), 3.39-3.35 (m, 2H), 1.36-1.27 (m, 12H); HRMS calculated for (M + H) 467.2289, found 467.2259.

EXAMPLE 17

[000193] This example illustrates the production ethyl 1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride.

[000194] Synthesis was conducted as in the preparation of ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride using ethyl 1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate (0.763 g, 1.53 mmol) and 4N HCl/dioxane (10 mL). A light yellow solid was obtained (0.685 g, 95.4% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.80 (d, 1H), 8.68 (d, 1H), 8.63 (s, 1H), 8.35 (dd, 1H), 8.13 (br s, 3H), 8.02 (dd, 1H), 7.93 (s, 2H), 7.85 (dd, 1H), 4.68 (t, 2H), 4.37 (q, 2H), 2.87-2.80 (m, 2H), 2.21-2.16 (m, 2H), 1.36 (t, 3H); HRMS calculated for (M + H) 396.1666, found 396.1660.

EXAMPLE 18

[000195] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride.

[000196] Synthesis was conducted as in the preparation of ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride using ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate (0.588 g, 1.21 mmol) and 4N HCl/dioxane (12 mL). A white solid was obtained (0.557 g, 100% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.97 (s, 1H), 9.86 (s, 1H), 8.87-8.85 (m, 2H), 8.62 (s, 1H), 8.48-8.41 (m, 5H), 8.15-8.08 (m, 2H), 7.98-7.90 (m, 2H), 4.89 (t, 2H), 4.39 (q, 2H), 3.43-3.36 (m, 2H), 1.37 (t, 3H); HRMS calculated for (M + H) 388.1768, found 388.1754.

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[000202] A flask was charged with ethyl 1-[2-[(tert-butoxycarbonyl)amino] ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.700 g, 1.78 mmol), 3-nitrophenylboronic acid (0.446 g, 2.67 mmol), 2M Na_2CO_3 (7 mL), toluene (20 mL), and [1, 1' bis(diphenylphosphino) ferrocene]dichloropalladium (II), 1:1 complex with dichloromethane [Pd[dppf]Cl_2·CH_2Cl_2 (0.116 g, 0.142 mmol)], then purged with N_2 and heated at 90°C for 20 h. The reaction mixture was filtered through Celite and the organic layer was concentrated. To this residue was added 4N HCl/dioxane (10.0 mL). After 2 h the reaction mixture was purified by Gilson RP HPLC (5-95% acetonitrile/water). The appropriate fractions were concentrated to a tacky residue, which was converted to the HCl salt using 4N HCl/dioxane and methanol. After stirring 1 h the reaction was concentrated to a brown solid (0.688 g, 85.1% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.01 (s, 1H), 8.80 (dd, 1H), 8.70-8.64 (m, 2H), 8.35-8.28 (m, 4H), 8.03 (d, 1H), 7.93 (s, 1H), 7.84 (dd, 1H), 4.87 (t, 2H), 4.38 (q, 2H), 3.39-3.33 (m, 2H), 1.36 (t, 3H); HRMS calculated for (M + H) 382.1510, found 382.1525.

EXAMPLE 22

[000203] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride.

[000204] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride using ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.700 g, 1.78 mmol), 4-methoxyphenylboronic acid (0.406 g, 2.67 mmol), 2M Na_2CO_3 (7 mL), toluene (20 mL), Pd[dppf]Cl_2·CH_2Cl_2 (0.116 g, 0.142 mmol), and 4N HCl/dioxane (10.0 mL). The product was isolated as a yellow solid (0.709 g, 90.7% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.77 (d, 1H), 8.65 (s, 1H), 8.35 (br s, 3H), 8.24 (d, 2H), 8.16 (d, 1H), 8.04 (s, 1H), 7.18 (d, 2H),

EXAMPLE 19

[000197] This example illustrates the production of ethyl 1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride.

[000198] Synthesis was conducted as for the preparation of ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride, using ethyl 1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate (0.404 g, 0.805 mmol) and 4N HCl/dioxane (10 mL). A yellow solid was obtained (0.357g, 93.5% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.92 (d, 1H), 9.72 (d, 1H), 8.84 (d, 1H), 8.79 (s, 1H), 8.40-8.36 (m, 2H), 8.16 (br s, 3H), 8.07-8.00 (m, 2H), 7.93-7.88 (m, 2H), 4.66 (t, 2H), 4.38 (q, 2H), 2.90-2.82 (m, 2H), 2.25-2.16 (m, 2H), 1.37 (t, 3H); HRMS calculated for (M + H) 402.1925, found 402.1937.

EXAMPLE 20

[000199] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-{2-[4-(hydroxymethyl)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate dihydrochloride.

[000200] Synthesis was conducted as for the preparation of ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride, using ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-{2-[4-(hydroxymethyl)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate (0.498 g, 1.07 mmol) and 4N HCl/dioxane (10 mL). A white solid was obtained (0.474g, 100% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.83 (d, 1H), 8.74 (s, 1H), 8.38 (br s, 3H), 8.29-8.20 (m, 3H), 8.08 (s, 1H), 7.57 (d, 2H), 4.90 (t, 2H), 4.62 (m, 2H), 4.39 (q, 2H), 3.40-3.35 (m, 2H), 1.36 (t, 3H); HRMS calculated for (M + H) 367.1765, found 367.1751.

EXAMPLE 21

[000201] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitro-phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride.

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4.89 (t, 2H), 4.38 (q, 2H), 3.87 (s, 3H), 3.42-3.38 (m, 2H), 1.36 (t, 3H), HRMS calculated for (M + H) 367.1765, found 367.1790.

EXAMPLE 23

[000205] This example illustrates the production of Ethyl 1-(2-aminoethyl)-3-{2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate dihydrochloride.

[000206] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride using ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.700 g, 1.78 mmol), 4-trifluoromethoxyphenylboronic acid (0.550 g, 2.67 mmol), 2M Na_2CO_3 (7 mL), toluene (20 mL), $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.116 g, 0.142 mmol), and 4N HCl/dioxane (10.0 mL). The product was isolated as a reddish-tan solid (0.821 g, 93.5% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.79 (d, 1H), 8.59 (s, 1H), 8.36-8.33 (m, 5H), 8.07 (d, 1H), 7.94 (s, 1H), 7.57 (d, 2H), 4.87 (t, 2H), 4.38 (q, 2H), 3.42-3.38 (m, 2H), 1.36 (t, 3H); HRMS calculated for (M + H) 421.1482, found 421.1482.

EXAMPLE 24

[000207] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-{2-[(E)-2-phenylethenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate dihydrochloride.

[000208] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride in using ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (1.044 g, 2.64 mmol), *trans*-2-phenylvinylboronic acid (0.587 g, 3.97 mmol), 2M Na_2CO_3 (10 mL), toluene (30 mL), $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.172 g, 0.211 mmol), and 4N HCl/dioxane (10.0 mL). The product was isolated as a yellow solid (1.213 g, >100% yield, 73.0% pure): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.79-8.72 (m, 2H), 8.36 (br s, 3H), 8.24-8.19 (m, 2H), 7.96 (s, 1H), 7.71 (d, 2H),

7.62-7.45 (m, 5H), 4.89 (t, 2H), 4.39 (q, 2H), 3.41-3.39 (m, 2H), 1.37 (t, 3H); HRMS calculated for (M + H) 363.1816, found 363.1807.

EXAMPLE 25

[000209] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate trifluoroacetate.

[000210] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride in using ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.758 g, 1.92 mmol), 4-dimethylaminophenylboronic acid (0.475 g, 2.88 mmol), 2M Na_2CO_3 (8 mL), toluene (23 mL), $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.126 g, 0.154 mmol), and 4N HCl/dioxane (10.0 mL). The TFA salt was isolated as a yellow solid (0.666 g, 70.3% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.64 (d, 1H), 8.46 (s, 1H), 8.07-8.04 (m, 5H), 7.95 (s, 1H), 7.88 (d, 1H), 6.86 (d, 2H), 4.85 (t, 2H), 4.38 (q, 2H), 3.47-3.37 (m, 2H), 3.09 (s, 6H), 1.36 (t, 3H); HRMS calculated for (M + H) 380.2081, found 380.2098.

EXAMPLE 26

[000211] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride.

[000212] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride, using ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.752g, 1.90 mmol), 3-methoxyphenylboronic acid (0.434 g, 2.86 mmol), 2M Na_2CO_3 (7 mL), toluene (20 mL), $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.124 g, 0.152 mmol), and 4N HCl/dioxane (10.0 mL). The product was isolated as an off-white solid (0.500 g, 60.0% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.81 (d, 1H), 8.67 (s, 1H), 8.37 (br s, 3H), 8.22 (d, 1H), 8.04 (s, 1H), 7.82-7.79 (m, 2H), 7.53 (dd, 1H), 7.18 (d, 1H), 4.89 (t, 2H), 4.38 (q, 2H), 3.89 (s, 3H), 3.42-3.38

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(m, 2H), 1.36 (t, 3H); HRMS calculated for (M + H) 367.1765, found 367.1755.

EXAMPLE 27

[000213] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-[2-(3-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride.

[000214] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride using ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl)-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (0.752g, 1.90 mmol), 3-hydroxyphenylboronic acid (0.629 g, 2.86 mmol), 2M Na_2CO_3 (7 mL), toluene (20 mL), $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.124 g, 0.152 mmol), and 4N HCl/dioxane (10.0 mL). The product was isolated as an off-white solid (0.381 g, 46.8% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.80 (d, 1H), 8.62 (s, 1H), 8.37 (br s, 3H), 8.22 (d, 1H), 8.04 (s, 1H), 7.62-7.58 (m, 2H), 7.41 (dd, 1H), 7.05 (dd, 1H), 4.89 (t, 2H), 4.38 (q, 2H), 3.89 (s, 3H), 3.42-3.36 (m, 2H), 1.36 (t, 3H); HRMS calculated for (M + H) 353.1608, found 353.1630.

EXAMPLE 28

[000215] This example illustrates the production of 2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000216] A flask was charged with ethyl 1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride (0.303 g, 0.659 mmol), NH_4OH (6 mL) and ethanol (3 mL). After stirring for 20 h, the reaction was filtered, and the solid rinsed with water, ethanol, and diethyl ether to obtain a white solid (0.178 g, 76.8% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.73 (s, 1H), 9.16 (s, 1H), 8.79 (s, 1H), 8.64 (s, 1H), 8.35 (s, 1H), 8.16-8.08 (m, 2H), 7.90-7.69 (m, 4H), 4.45 (br s, 2H), 3.69 (br s, 2H); HRMS calculated for (M + H) 342.1349, found 342.1365.

EXAMPLE 29

[000217] This example illustrates the production of 2-(2-quinolin-3-ylpyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000218] Synthesis was conducted as it was for the production of 2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one using ethyl 1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride (0.144 g, 0.303 mmol), NH_4OH (6mL), and ethanol (3 mL). A white solid was obtained (0.046 g, 43% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.72 (d, 1H), 9.16 (d, 1H), 8.77 (d, 1H), 8.61 (s, 1H), 8.35 (br s, 1H), 8.15-8.07 (m, 2H), 7.88-7.79 (m, 2H), 7.71-7.66 (m, 2H), 4.55 (t, 2H), 3.29-3.23 (m, 2H), 2.22-2.18 (m, 2H); HRMS calculated for (M + H) 356.1506, found 356.1525.

EXAMPLE 30

[000219] This example illustrates the production of 2-[2-[4-(hydroxymethyl)phenyl] pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000220] Synthesis was conducted as it was for the production of 2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one using ethyl 1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.202 g, 0.459 mmol), NH_4OH (8 mL), and ethanol (4 mL). A white solid was obtained (0.098 g, 66% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.67 (d, 1H), 8.36-8.32 (m, 2H), 8.15 (d, 2H), 7.78 (d, 1H), 7.64 (s, 1H), 7.45 (d, 2H), 5.27 (t, 1H), 4.57 (d, 2H), 4.42 (t, 2H), 3.70-3.66 (m, 2H); HRMS calculated for (M + H) 321.1346, found 321.1333.

EXAMPLE 31

[000221] This example illustrates the production of 2-[2-(3-methoxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000222] Synthesis was conducted as it was for the production of 2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one using ethyl 1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-

pyrazole-5-carboxylate dihydrochloride (0.253 g, 0.575 mmol), NH_4OH (8 mL), and ethanol (4 mL). An off-white solid was obtained (0.160 g, 86.8% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (s, 1H), 8.37-8.32 (m, 2H), 7.80-7.68 (m, 4H), 7.42 (dd, 1H), 7.03 (d, 1H), 4.42 (t, 2H), 3.86 (s, 3H), 3.69-3.65 (m, 2H); HRMS calculated for (M + H) 321.1346, found 321.1344.

EXAMPLE 32

[000223] This example illustrates the production of 2-[2-(3-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000224] Synthesis was conducted as it was for the production of 2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one using ethyl 1-(2-aminoethyl)-3-[2-(3-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.304 g, 0.715 mmol), NH_4OH (10 mL), and ethanol (5 mL). An off-white solid was obtained (0.178 g, 81.1% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.56 (br s, 1H), 8.66 (d, 1H), 8.32-8.28 (m, 2H), 7.79 (s, 1H), 7.63-7.59 (m, 3H), 7.30 (dd, 1H), 6.85 (d, 1H), 4.42 (t, 2H), 3.69-3.64 (m, 2H); HRMS calculated for (M + H) 307.1190, found 307.1214.

EXAMPLE 33

[000225] This example illustrates the production of 2-[2-(3-nitrophenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride.

[000226] Synthesis was conducted as it was for the production of 2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate using ethyl 1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.253 g, 0.540 mmol), NH_4OH (8 mL), and ethanol (4 mL). The isolated TFA salt was converted to the HCl salt using methanol and 4N HCl/dioxane. After 0.5 h, the suspension was concentrated and the solid rinsed with diethyl ether to afford a white solid (0.140 g, 65.2% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.78 (d, 1H), 8.65 (d, 1H), 8.60 (s, 1H), 8.39-8.33 (m, 2H), 8.00 (dd, 1H),

7.84 (dd, 1H), 7.74 (s, 1H), 4.54 (t, 2H), 3.27-3.21 (m, 2H), 2.20-2.15 (m, 2H); HRMS calculated for (M + H) 342.1349, found 342.1365.

EXAMPLE 34

[000227] This example illustrates the production of 2-{2-[4-(trifluoromethoxy)-phenyl]pyridin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000228] Synthesis was conducted as it was for the production of 2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate using ethyl 1-(2-aminoethyl)-3-{2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate dihydrochloride (0.439 g, 0.889 mmol), NH_4OH (8 mL), and ethanol (4 mL). An off-white solid was obtained (0.181 g, 43.0% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.72 (d, 1H), 8.45 (s, 1H), 8.33-8.30 (m, 3H), 7.88 (d, 1H), 7.69 (s, 1H), 7.51 (d, 2H), 4.43 (q, 2H), 3.70-3.64 (m, 2H); HRMS calculated for (M + H) 375.1063, found 375.1068.

EXAMPLE 35

[000229] This example illustrates the production of 2-[2-[(E)-2-phenylvinyl]pyridin- 4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000230] Synthesis was conducted as it was for the production of 2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate using ethyl 1-(2-aminoethyl)-3-[2-[(E)-2-phenylvinyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate dihydrochloride (0.610 g, 1.40 mmol), NH_4OH (10 mL), and ethanol (5 mL). A yellow solid was obtained (0.352 g, 58.4% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (d, 1H), 8.40 (br s, 2H), 7.97-7.92 (m, 2H), 7.71-7.68 (m, 3H), 7.49-7.37 (m, 4H), 4.45 (t, 2H), 3.70-3.66 (m, 2H); HRMS calculated for (M + H) 317.1397, found 317.1405.

EXAMPLE 36

[000231] This example illustrates the production of 2-{2-[4-(dimethylamino)phenyl]-pyridin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000232] Synthesis was conducted as it was for the production of 2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate using ethyl 1-(2-aminoethyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate trifluoroacetate (0.350 g, 708 mmol), NH_4OH (8 mL), and ethanol (4 mL). A yellow solid was obtained (0.204 g, 64.5% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.61 (d, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 8.03 (d, 2H), 7.96 (d, 1H), 7.86 (s, 1H), 6.88 (d, 2H), 4.46 (t, 2H), 3.71-3.66 (m, 2H), 3.05 (s, 6H); HRMS calculated for (M + H) 334.1662, found 334.1673.

EXAMPLE 37

[000233] This example illustrates the production of 2-[2-(4-methoxyphenyl)-pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000234] Synthesis was conducted as it was for the production of 2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate using ethyl 1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.368 g, 0.838 mmol), NH_4OH (8 mL), and ethanol (4 mL). A white solid was obtained (0.225 g, 61.8% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (d, 1H), 8.45 (s, 1H), 8.36 (s, 1H), 8.13 (d, 2H), 7.93 (d, 1H), 7:76 (s, 1H), 7.12 (d, 2H), 4.44 (t, 2H), 3.85 (s, 3H), 3.71-3.66 (m, 2H); HRMS calculated for (M + H) 321.1346, found 321.1359.

EXAMPLE 38

[000235] This example illustrates the production of 2-[2-(3-nitrophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000236] Synthesis was conducted as it was for the production of 2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate using ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.350 g, 0.771 mmol), NH_4OH (8 mL), and ethanol (4 mL). A beige solid was obtained (0.152 g, 43.8% yield): ^1H

NMR (DMSO-d_6 / 300 MHz) δ 9.00 (s, 1H), 8.75 (d, 1H), 8.66 (d, 1H), 8.32-8.28 (m, 2H), 7.89 (d, 1H), 7.81 (dd, 1H), 7.73 (s, 1H), 4.43 (t, 2H), 3.70-3.65 (m, 2H); HRMS calculated for (M + H) 336.1091, found 336.1068.

EXAMPLE 39

[000237] This example illustrates the production of 2-[2-(3,4-difluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000238] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride using 2-(2-chloropyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (0.175 g, 0.702 mmol), 3,4-difluorophenylboronic acid (0.167 g, 1.05 mmol), 2M Na_2CO_3 (2 mL), toluene (7 mL), and $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.046 g, 0.057 mmol). The TFA salt was isolated as a white solid (0.076 g, 25% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.66 (d, 1H), 8.42 (s, 1H), 8.32-8.23 (m, 2H), 8.09 (d, 1H), 7.82 (s, 1H), 7.69 (s, 1H), 7.55 (dd, 1H), 4.41 (t, 2H), 3.69-3.64 (m, 2H); HRMS calculated for (M + H) 327.1052, found 327.1078.

EXAMPLE 40

[000239] This example illustrates the production of 2-[2-(3,4-dichlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000240] Synthesis was conducted as for the production of ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride using 2-(2-chloropyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (0.175 g, 0.702 mmol), 3,4-dichlorophenylboronic acid (0.200 g, 1.05 mmol), 2M Na_2CO_3 (2 mL), toluene (7 mL), and $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.046 g, 0.057 mmol). The TFA salt was obtained as a gray solid (0.016 g, 4.9% yield): ^1H NMR (DMSO-d_6, TFA / 300 MHz) δ 8.81 (d, 1H), 8.66 (s, 1H), 8.42-8.34 (m, 2H), 8.28-8.18 (m, 2H), 7.87-7.85 (m, 2H), 4.45 (t, 2H), 3.71-3.64 (m, 2H), HRMS calculated for (M + H) 359.0461, found 359.0476.

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EXAMPLE 41

[000241] This example illustrates the production of 1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride.

[000242] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate (0.253 g, 0.539 mmol) and $LiOH \cdot H_2O$ (0.0679 g, 1.62 mmol. The isolated TFA salt was a tacky solid, and thus converted to the HCl salt using methanol and 4N HCl/dioxane. After 0.5 h, the suspension was concentrated and the solid rinsed with diethyl ether to afford a white solid (0.223 g, 94.6% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.79 (d, 1H), 8.68 (d, 1H), 8.60 (s, 1H), 8.34 (dd, 1H), 8.11 (br s, 3H), 7.99 (dd, 1H), 7.88-7.81 (m, 2H), 4.68 (t, 2H), 2.86-2.79 (m, 2H), 2.20-2.15 (m, 2H); HRMS calculated for (M + H) 368.1353, found 368.1336.

EXAMPLE 42

[000243] This example illustrates the production of 1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000244] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride (0.211 g, 0.457 mmol) and $LiOH \cdot H_2O$ (0.077 g, 1.8 mmol). A pink solid was obtained (0.150 g, 69.4% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.75 (s, 1H), 9.23 (d, 1H), 8.82 (d, 1H), 8.69 (s, 1H), 8.17-8.10 (m, 2H), 8.01-7.94 (m, 3H), 7.89-7.83 (m, 2H), 7.72 (dd, 1H), 4.86 (t, 2H), 3.44-3.38 (m, 2H); HRMS calculated for (M + H) 360.1455, found 360.1466.

EXAMPLE 43

[000245] This example illustrates the production of 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride.

[000246] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.262 g, 0.516 mmol) and $LiOH \cdot H_2O$ (0.097 g, 2.3 mmol). The isolated TFA salt converted to the HCl salt using methanol and 4N HCl/dioxane. After 0.5 h, the suspension was concentrated and the solid rinsed with diethyl ether to afford a yellow solid (0.102 g, 46.5% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.01 (s, 1H), 8.80 (d, 1H), 8.70-8.64 (m, 2H), 8.35-8.28 (m, 4H), 8.02 (d, 1H), 7.89-7.82 (m, 2H), 3.39-3.33 (m, 2H); HRMS calculated for (M + H) 354.1197, found 354.1176.

EXAMPLE 44

[000247] This example illustrates the production of 1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000248] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.260 g, 0.591 mmol) and $LiOH \cdot H_2O$ (0.099 g, 2.4 mmol). A pale yellow solid was obtained (0.212 g, 79.4% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (d, 1H), 8.42 (s, 2H), 8.15 (d, 1H), 8.00 (br s, 3H), 7.88-7.84 (m, 2H), 7.09 (d, 2H), 4.84 (t, 2H), 3.84 (s, 3H), 3.38-3.42 (m, 2H); HRMS calcd for (M + H) 339.1452, found 339.1472.

EXAMPLE 45

[000249] This example illustrates the production of 1-(2-aminoethyl)-3-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000250] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(2-aminoethyl)-3-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-

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1H-pyrazole-5-carboxylate dihydrochloride (0.257 g, 0.521 mmol) and LiOH•H_2O (0.097 g, 2.3 mmol). A beige solid was obtained (0.088 g, 34% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.73 (d, 1H), 8.50 (s, 1H), 8.32 (d, 2H), 8.01 (br s, 3H), 7.88 (d, 1H), 7.81 (s, 1H), 7.51 (d, 2H), 4.84 (t, 2H), 3.42-3.38 (m, 2H); HRMS calculated for (M + H) 393.1169, found 393.1189.

EXAMPLE 46

[000251] This example illustrates the production of 1-(2-aminoethyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000252] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetateusing ethyl 1-(2-aminoethyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate trifluoroacetate (0.238 g, 0.482 mmol) and LiOH•H_2O (0.088 g, 2.1 mmol). A neon orange solid was obtained (0.150 g, 67.0% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.64 (d, 1H), 8.46 (s, 1H), 8.07-8.04 (m, 5H), 7.91-7.88 (m, 2H), 6.86 (d, 2H), 4.86 (t, 2H), 3.43-3.37 (m, 2H), 3.03 (s, 6H); HRMS calcd for (M + H) 352.1768, found 352.1770.

EXAMPLE 47

[000253] This example illustrates the production of 1-(2-aminoethyl)-3-[2-[(E)-2-phenylethenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000254] Synthesis was conducted as in the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(2-aminoethyl)-3-[2-[(E)-2-phenylvinyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.311 g, 0.714 mmol) and LiOH•H_2O (0.120 g, 2.86 mmol). The TFA salt was isolated as a light yellow solid (0.220 g, 68.7% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.68 (d, 1H), 8.26 (s, 1H), 8.03 (br s, 3H), 7.89-7.84 (m, 2H), 7.73-7.68 (m, 3H),

7.45-7.36 (m, 4H), 4.89 (t, 2H), 3.41-3.39 (m, 2H); HRMS calculated for (M + H) 335.1503, found 335.1496.

EXAMPLE 48

[000255] This example illustrates the production of 1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid dihydrochloride.

[000256] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride (0.134 g, 0.282 mmol) and LiOH•H_2O (0.047 g, 1.1 mmol). The TFA salt was converted to the HCl salt using methanol and 4N HCl/dioxane. After 0.5 h, the suspension was concentrated and the solid rinsed with diethyl ether to afford a yellow solid (0.086 g, 68% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.92 (d, 1H), 9.95 (s, 1H), 9.83 (s, 1H), 8.44-8.41 (m, 2H), 8.17-8.09 (m, 4H), 8.03 (d, 1H), 7.94 (dd, 1H), 7.86 (s, 1H), δ 4.69 (t, 2H), 2.90-2.82 (m, 2H), 2.25-2.16 (m, 2H); HRMS calculated for (M + H) 374.1612, found 374.1622.

EXAMPLE 49

[000257] This example illustrates the production of 1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride.

[000258] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.167 g, 0.379 mmol) and LiOH•H_2O (0.064 g, 1.5 mmol). The TFA salt was converted to the HCl salt using methanol and 4N HCl/dioxane. After 0.5 h, the suspension was concentrated and the solid rinsed with diethyl ether to afford a pale pink solid (0.069 g, 70% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.80 (d, 1H), 8.67 (s, 1H), 8.33 (br s, 3H), 8.22-8.19 (m, 3H), 8.00 (s, 1H), 7.55 (d, 2H), 4.89 (t, 2H), 4.62 (m, 2H), 3.40-3.35 (m, 2H); HRMS calculated for (M + H) 339.1452, found 339.1435.

EXAMPLE 50

[000259] This example illustrates the production of 1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000260] Synthesis was conducted as for the preparation of 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate, using ethyl 1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (0.179 g, 0.407 mmol) and $LiOH \cdot H_2O$ (0.105 g, 2.50 mmol). An off-white solid was obtained (0.168 g, 91.2% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.72 (d, 1H), 8.43 (s, 1H), 8.00 (br s, 3H), 7.88 (d, 1H), 7.83 (s, 1H), 7.78-7.74 (m, 2H), 7.44 (dd, 1H), 7.06 (dd, 1H), 4.84 (t, 2H), 3.85 (s, 3H), 3.44-3.38 (m, 2H); HRMS calculated for (M + H) 339.1452, found 339.1469.

EXAMPLE 51

[000261] This example illustrates the production of 1-(2-aminoethyl)-N-hydroxy-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxamide trifluoroacetate.

[000262] Freshly made sodium methoxide (3.48 M, 0.27 mL) was added dropwise to a stirring solution of hydroxylamine hydrochloride (0.039 mL, 0.94 mmol) in methanol (1 mL) maintained at 40°C. The white slurry was cooled to room temperature, and then a solution of ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate (0.400 g, 0.857 mmol) in methanol (5 mL) was added. After stirring for 48 h, 7 mL of 4N HCl (aq) was added and the reaction stirred for 20 h. Purification by Gilson RP HPLC (5-95% acetonitrile/water) afforded a pink solid (0.129 g, 32.1% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 11.53 (br s, 1H), 8.73 (d, 1H), 8.31 (s, 1H), 8.11-8.01 (m, 5H), 7.75 (d, 1H), 7.52-7.46 (m, 3H), 4.77 (t, 2H), 4.58 (s, 2H), 3.42-3.35 (m, 2H); HRMS calculated for (M + H) 354.1561, found 354.1538.

EXAMPLE 52

[000263] This example illustrates the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride.

[000264] A flask was charged with 1. 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol), pyrazole (0.325 g, 4.78 mmol), and sodium hydride (0.229 g, 5.73 mmol) in 6 mL anhydrous DMF and stirred under N_2 for 60 h at 138°C. The reaction was then quenched with 1N HCl (aq) and purified by Gilson RP HPLC (5-95% acetonitrile/water). The appropriate fractions were concentrated and converted to the HCl salt using methanol and 4N HCl/dioxane. The mixture was concentrated to a light yellow solid (0.028 g, 8.2% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.64 (d, 1H), 8.48 (d, 1H), 8.35 (br s, 2H), 7.85 (s, 1H), 7.77 (d, 1H), 7.45 (s, 1H), 6.59 (s, 1H), 4.53 (t, 2H), 3.26-3.20 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculated for (M + H) 295.1302, found 295.1285.

EXAMPLE 53

[000265] This example illustrates the production of 2-[2-(1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride.

[000266] Synthesis was conducted as for the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride using 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol) and imidazole, sodium derivative (0.431 g, 4.78 mmol). A white solid was obtained (0.074 g, 23% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 10.0 (s, 1H), 8.62 (d, 1H), 8.55 (s, 1H), 8.48 (s, 1H), 8.41 (br s, 1H), 7.99 (d, 1H), 7.90 (s, 1H), 7.65 (s, 1H), 4.53 (t, 2H), 3.28-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculated for (M + H) 295.1302, found 295.1290.

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EXAMPLE 54

[000267] This example illustrates the production of 2-[2-(1H-pyrrol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate.

[000268] Synthesis was conducted as for the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride, using 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol), pyrrole (0.334 mL, 4.78 mmol), and sodium hydride (0.229 g, 5.73 mmol). The TFA salt was isolated as a black solid (0.128 g, 32.7% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.42 (d, 1H), 8.34 (br s, 1H), 8.05 (s, 1H), 7.79 (br s, 2H), 7.67-7.64 (m, 2H), 6.30 (br s, 2H), 4.52 (t, 2H), 3.28-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculated for (M.+ H) 294.1349, found 294.1348.

EXAMPLE 55

[000269] This example illustrates the production of 2-[2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a] [1,4] diazepin-4-one hydrochloride.

[000270] Synthesis was conducted as for the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride, using 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol), 4-methylimidazole (0.393 g, 4.78 mmol), and sodium hydride (0.229 g, 5.73 mmol). A brown solid was obtained (0.053 g, 16% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.88 (s, 1H), 8.60 (d, 1H), 8.40 (br s, 2H), 8.28 (s, 1H), 7.97 (d, 1H), 7.63 (s, 1H), 4.53 (t, 2H), 3.29-3.22 (m, 2H), 2.36 (s, 3H), 2.22-2.16 (m, 2H); HRMS calculated for (M + H) 309.1458, found 309.1462.

EXAMPLE 56

[000271] This example illustrates the production of 2-[2-(4-phenyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate.

[000272] Synthesis was conducted as for the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride, using 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol), 4-phenylimidazole (0.690 g, 4.76 mmol), and sodium hydride (0.229 g, 5.73 mmol). The TFA salt was isolated as a white solid (0.060 g, 13% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.17 (s, 1H), 8.76 (s, 1H), 8.57 (d, 1H), 8.37-8.32 (m, 2H), 7.93-7.88 (m, 3H), 7.65 (s, 1H), 7.47 (dd, 2H), 7.36-7.34 (m, 1H), 4.54 (t, 2H), 3.29-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculated for (M + H) 371.1615, found 371.1626.

EXAMPLE 57

[000273] This example illustrates the production of 2-[2-(4-methyl-1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate.

[000274] Synthesis was conducted as it was for the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride, using 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol), 4-methylpyrazole (0.40 mL, 4.8 mmol), and sodium hydride (0.229 g, 5.73 mmol). The TFA salt was isolated as a white solid (0.068 g, 16% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.45-8.29 (m, 4H), 7.72 (m, 1H), 7.66 (s, 1H), 7.42 (s, 1H), 4.54 (t, 2H), 3.25-3.20 (m, 2H), 2.20-2.11 (m, 5H); HRMS calculated for (M + H) 309.1458, found 309.1448.

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EXAMPLE 58

[000275] This example illustrates the production of 2-[2-(1H-1,2,4-triazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a] [1,4]diazepin-4-one hydrochloride.

[000276] Synthesis was conducted as it was for the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride, using 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol) and 1,2,4-triazole, sodium derivative (0.435 g, 4.78 mmol). A white solid was obtained (0.157 g, 48.4% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.40 (s, 1H), 8.55 (d, 1H), 8.37-8.33 (m, 2H), 8.27 (s, 1H), 7.90 (dd, 1H), 7.50 (s, 1H), 4.53 (t, 2H), 3.25-3.20 (m, 2H), 2.22-2.14 (m, 2H); HRMS calcd for (M + H) 296.1254, found 296.1244.

EXAMPLE 59

[000277] This example illustrates the production of 2-[2-(1H-1,2,3-triazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a] [1,4]diazepin-4-one hydrochloride.

[000278] Synthesis was conducted as it was for the production of 2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride, using 2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.251 g, 0.960 mmol), 1,2,3-triazole (0.28 mL, 4.8 mmol), and sodium hydride (0.229 g, 5.73 mmol). A white solid was obtained (0.116 g, 36.0% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.89 (s, 1H), 8.61 (d, 1H), 8.52 (s, 1H), 8.37 (br s, 1H), 8.01-7.96 (m, 2H), 7.55 (s, 1H), 4.54 (t, 2H), 3.29-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calcd for (M + H) 296.1254, found 296.1243.

EXAMPLE 60

[000279] This example illustrates the production of ethyl 1-[3-[(tert-butoxycarbonyl)-amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate.

[000280] To a cooled (0°C) solution of ethyl 3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylatein anhydrous DMF (35 mL) was added lithium *t*-butoxide (1M in THF, 6.6 mL) dropwise. The reaction stirred for 30 min, and then a solution of *tert*-butyl 3-bromopropylcarbamate (1.57 g, 6.60 mmol) and sodium iodide (0.989 g, 6.60 mmol) in anhydrous DMF (10 mL) was added dropwise. The reaction was allowed to stir and warm to room temperature for 4 h. The reaction was then poured into water and brine and extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Chromatographic purification (15% ethyl acetate/hexane) afforded a yellow oil (1.13 g, 63.7% yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 7.81 (d, 2H), 7.27 (s, 1H), 6.87 (t, 1H), 6.79 (d, 2H), 4.52 (t, 2H), 4.37 (q, 2H), 3.80 (s, 3H), 3.30-2.94 (m, 2H), 1.96-1.91 (m, 2H), 1.39-1.33 (m, 12H); HRMS calculated for (M + H) 404.2180, found 404.2190.

EXAMPLE 61

[000281] This example illustrates the production of 1-[3-[(tert-butoxycarbonyl)-amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid.

[000282] A solution of ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.467 g, 1.16 mmol) and $LiOH•H_2O$ (0.097 g, 2.32 mmol) in 12 mL of THF/H_2O (1:1) stirred at room temperature for 3 h. The reaction mixture was concentrated to the aqueous phase, then diluted with 0.1N HCl and extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to a pale yellow solid (0.359 g, 82.3%yield): ^1H NMR (DMSO-d_6 / 300 MHz) δ 7.71 (d, 2H), 7.01-6.94 (m, 3H), 6.88 (s, 1H), 4.62 (t, 2H), 3.80 (s, 3H), 2.94-2.90 (m, 2H), 1.91-1.84 (m, 2H), 1.39 (s, 9H); HRMS calculated for (M + H) 376.1867, found 376.1906.

EXAMPLE 61

[000283] This example illustrates the production of 1-(3-aminopropyl)-3-(4-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid dihydrochloride.

[000284] To a cooled (-78 °C) solution of 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (0.262 g, 0.70 mmol) in anhydrous dichloromethane (7 mL) was added boron tribromide (1.0M in CH_2Cl_2, 7.0 mL) dropwise. After 1 h the reaction was carefully quenched with water, then concentrated to the aqueous layer and purified by Gilson RP HPLC (5-95% acetonitrile/water). The appropriate fractions were concentrated. The residue was converted to the HCl salt using 4N HCl/dioxane and methanol. After stirring 1 h, the mixture was concentrated to a white solid (0.238 g, 100% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.07 (br s, 3H), 7.67 (d, 2H), 7.18 (s, 1H), 6.83 (d, 2H), 4.59 (t, 2H), 2.84-2.78 (m, 2H), 2.18-2.08 (m, 2H); HRMS calculated for (M + H) 262.1186, found 262.1195.

EXAMPLE 62

[000285] This example illustrates the production of ethyl 1-(3-aminopropyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate hydrochloride.

[000286] To a flask charged with ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.588 g, 1.46 mmol) was added 4N HCl/dioxane (5 mL). After 1 h the reaction mixture was filtered and rinsed with diethyl ether to yield a white solid (0.443 g, 89.4% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.06 (br s, 3H), 7.81 (d, 2H), 7.32 (s, 1H), 7.00 (d, 2H), 4.61 (t, 2H), 4.37 (q, 2H), 3.80 (s, 3H), 2.87-2.80 (m, 2H), 2.20-2.11 (m, 2H), 1.36 (t, 3H), HRMS calcd for (M + H) 304.1656, found 304.1665.

EXAMPLE 63

[000287] This example illustrates the production of 2-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000288] To a flask charged with ethyl 1-(3-aminopropyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate hydrochloride (0.418 g, 1.23 mmol) was added NH_4OH (20 mL) and ethanol (10 mL). After stirring for 18h, the reaction was filtered, and the white solid rinsed with diethyl ether to afford a white solid (0.243 g, 76.8% yield): ^{1}H NMR (DMSO-d_6 / 300

MHz) δ 8.28 (br s, 1H), 7.77 (d, 2H), 7.10 (s, 1H), 6.98 (d, 2H), 4.45 (t, 2H), 3.80 (s, 3H), 3.26-3.21 (m, 2H), 2.20-2.13 (m, 2H); HRMS calculated for (M + H) 258.1242, found 258.1237.

EXAMPLE 64

[000289] This example illustrates the production of 2-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000290] Synthesis was conducted as it was for the preparation of 1-(3-amino-propyl)-3-(4-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid dihydrochloride using ethyl 1-(3-aminopropyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate hydrochloride (0.182 g, 0.70 mmol) and boron tribromide (7.0 mL). Purification by Gilson RP HPLC (5-95% acetonitrile/water) afforded a white solid (0.078 g, 46% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.55 (br s, 1H), 8.25 (br s, 1H), 7.65 (d, 2H), 7.03 (s, 1H), 6.80 (d, 2H), 4.44 (t, 2H), 3.26-3.21 (m, 2H), 2.18-2.13 (m, 2H); HRMS calculated for (M + H) 244.1081, found 244.1049.

EXAMPLE 65

[000291] This example illustrates the production of ethyl 1-[3-[(tert-butoxy-carbonyl)amino]propyl]-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylate.

[000292] Synthesis was conducted as it was for the preparation of ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate, using ethyl 3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylate (2.01 g, 8.17 mmol), lithium *t*-butoxide (12.3 mL), *tert*-butyl 3-bromopropylcarbamate (2.92 g, 12.3 mmol) and sodium iodide (1.84 g, 12.3 mmol). Flash chromatography (12% ethyl acetate/hexane) afforded a yellow oil, which was triturated with diethyl ether to yield a pale yellow solid (1.47 g, 45.0% yield): HRMS calculated for (M + H) 404.2180, found 404.2206.

EXAMPLE 66

[000293] This example illustrates the production of 1-[3-[(tert-butoxycarbonyl)-amino]propyl]-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylic acid.

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[000294] Synthesis was conducted as it was for the preparation of 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid using ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.610 g, 1.51 mmol) and LiOH•H_2O (0.127 g, 3.02 mmol). An off-white solid was obtained (0.565g, 100% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 13.47 (br s, 1H), 7.46-7.32 (m, 4H), 6.93-6.86 (m, 2H), 4.56 (t, 2H), 3.83 (s, 3H), 3.01-2.95 (m, 2H), 1.96-1.90 (m, 2H), 1.39 (s, 9H); HRMS calculated for (M + H) 376.1873, found 376.1896.

EXAMPLE 67

[000295] This example illustrates the production of 1-(3-aminopropyl)-3-(3-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000296] Synthesis was conducted as it was for the preparation of 1-(3-amino-propyl)-3-(4-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid dihydrochloride, using 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (0.496 g, 1.32 mmol) and boron tribromide (1.0M in CH_2Cl_2, 13.0 mL). The TFA salt was isolated as an off-white solid (0.353 g, 71.3% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 13.62 (br s, 1H), 9.56 (br s, 1H), 7.80 (br s, 3H), 7.27-7.23 (m, 4H), 6.77 (d, 1H), 4.63 (t, 2H), 2.89-2.81 (m, 2H), 2.17-2.07 (m, 2H); HRMS calculated for (M + H) 262.1192, found 262.1223.

EXAMPLE 68

[000297] This example illustrates the production of 2-(3-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000298] Synthesis was conducted as it was for the preparation of ethyl 1-(3-aminopropyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate hydrochloride, using ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.737 g, 1.83 mmol) and 4N HCl/dioxane (10 mL). The resulting colorless oil was subjected to conditions described for the production of 2-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one, sing NH_4OH (12 mL) and ethanol (6 mL). An off-white solid was obtained: ^{1}H NMR (DMSO-d_6 /

300 MHz) δ 8.29 (br s, 1H), 7.34-7.45 (m, 3H), 7.23 (s, 1H), 6.90 (dd, 1H), 4.48 (t, 2H), 3.83 (s, 3H), 3.26-3.21 (m, 2H), 2.22-2.14 (m, 2H); HRMS calculated for (M + H) 258.1242, found 258.1232.

EXAMPLE 69

[000299] This example illustrates the production of 2-(3-hydroxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000300] Synthesis was conducted as it was for the preparation of 1-(3-amino-propyl)-3-(4-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid dihydrochloride, using 2-(3-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one (0.325 g 1.26 mmol) and boron tribromide (13.0 mL). Purification by Gilson RP HPLC (5-95% acetonitrile/ water) afforded a white solid (0.194 g, 63.3% yield): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.45 (br s, 1H), 8.28 (br s, 1H), 7.28-7.19 (m, 3H), 7.08 (s, 1H), 6.75-6.72 (m, 1H), 4.47 (t, 2H), 3.26-3.21 (m, 2H), 2.20-2.16 (m, 2H); HRMS calculated for (M + H) 244.1086, found 244.1115.

EXAMPLE 70

[000301] This example illustrates the production of 1-(3-[[2-(4-bromophenyl)ethyl]-amino}propyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid hydrochloride.

[000302] A single neck round bottom flask was charged with ethyl 3-pyridin-4-yl-1H-pyrazole-5-carboxylate (1.0 g, 4.6 mmol) and 30 mL DMF. The solution was cooled to -40°C in a dry ice/ CH_3CN bath. A 1 M solution of lithium *t*-butoxide in THF (6.9 mL, 6.9 mmol) was added dropwise over 5 minutes. After stirring at –40 °C for 30 minutes, a solution of 3-[[2-(4-bromophenyl)ethyl](tert-butoxycarbonyl)amino]propyl methanesulfonate (3.0 g, 6.9 mmol) in 10 mL DMF was added dropwise over 5 minutes. After 1 hour the reaction was allowed to warmed to ambient temperature and stirred for 18 hours. The reaction mixture was concentrated in vacuo, and the residue taken up in ethyl acetate. This was washed 3 times with brine, dried over magnesium sulfate, and concentrated to a brown oil. The oil was treated with 20 mL of a 4 N HCl in dioxane solution, and stirred for 30 minutes to remove the protecting group. After concentrating in vacuo

the crude mixture was treated with 20 mL of a 2.5 N sodium hydroxide solution. The mixture was heated to 100 °C for 1 hour to hydrolyze the ester. The resulting product mixture was concentrated in vacuo to half the volume, and then chromatographed on a Gilson reverse phase HPLC eluting with an acetonitrile/water gradient (5-70% CH_3CN over 15 minutes) to provide the desired product as a TFA salt. The salt was taken up in methanol, and treated with 10 mL of a 4 N solution of HCl in dioxane to convert to the HCl salt. Crystallization from diethyl ether afforded 1.30g (56%) of the title compound as a tan solid. LCMS showed a single peak with m/z 429 (M+H). ^{1}H nmr (DMSO-d_6/300 MHz) δ 9.48 (broad s, 2H), 8.94 (d, 2H), 8.46 (d, 2H), 7.90 (s, 1H), 7.50 (d, 2H), 7.22 (d, 2H), 4.71 (t, 2H), 3.20-2.88 (m, 6H), 2.30 (m, 2H), ES^+ HRMS calculated for M+H 429.0921, observed 429.0934.

EXAMPLE 71

[000303] This example illustrates the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride.

[000304] Step 1. Preparation of ethyl 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride.

[000305] This compound was prepared as part of a parallel library. A reaction tube was charged with ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (550 mg, 1.35 mmol) and 4-methoxybenzene boronic acid (307 mg, 2.02 mmol). The mixture was purged with N_2, and then 16 mL toluene and 6 mL of a 2M sodium carbonate solution were added. The reaction mixture was again purged with N_2. To this stirring mixture [1,1'-bis(diphenyl phosphino)ferrocene] dichloropalladium II·CH_2Cl_2 (88 mg, 0.11 mmol) was added, and the reaction heated to 80°C for 18 hours. The water layer was decanted, and the organic layer filtered through celite, and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo*, and the residue treated with 10 mL of a 4 N HCl in dioxane solution for 1 hour. The product was concentrated *in vacuo*, washed with diethyl ether, and air

dried to afford 673 mg (quantitative) of the desired ester. LCMS showed one major peak with m/z 381 (M+H).

[000306] Step 2. Preparation of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride.

[000307] This compound was prepared as part of a parallel library. A reaction tube was charged with ethyl 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride (200 mg, 0.44 mmol) and 10 mL of a 2.5 N NaOH solution. The mixture was heated to 100°C for 30 minutes, and concentrated *in vacuo*. The product mixture was chromatographed on a Gilson reverse phase HPLC eluting with an acetonitrile/water gradient (5-70% CH_3CN over 15 minutes). The fractions containing the desired product were combined and concentrated. The oil was taken up in methanol and treated with 5 mL of a 4 N HCl in dioxane solution to obtain the HCl salt. The solution was concentrated to dryness, washed with diethyl ether, and air dried to afford 196 mg (quantitative) of the title carboxylic acid. LCMS showed a single peak with m/z 353 (M+H). ES^+ HR MS calculated for M+H 353.1608, observed 353.1640.

EXAMPLE 72

[000308] This example illustrates the production of 1-(3-aminopropyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride.

[000309] The preparation of 1-(3-aminopropyl)-3-[2-[4-(dimethylamino)phenyl]-pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride was carried out in the same manner as that described for the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride, using 4-dimethyl(amino)phenyl boronic acid. Purification afforded the title carboxylic acid as an orange solid. 6% yield over 2 steps. LCMS showed a single peak with m/z 366 (M+H). ES^+ HR MS calculated for M+H 366.1925, observed 366.1918.

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EXAMPLE 73

[000310] This example illustrates the production of 1-(3-aminopropyl)-3-{2-[3-(hydroxymethyl)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylic acid hydrochloride.

[000311] The preparation of 1-(3-aminopropyl)-3-[2-[3-(hydroxymethyl)phenyl]-pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride was carried out in the same manner as that described for the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride, using 3-hydroxymethylphenyl boronic acid. Purification afforded the title carboxylic acid as a brown solid. 5% yield over 2 steps. LCMS showed a single peak with m/z 353 (M+H). ES^+ HR MS calculated for M+H 353.1608, observed 353.1608.

EXAMPLE 74

[000312] This example illustrates the production of 1-(3-aminopropyl)-3-{2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylic acid hydrochloride.

[000313] The preparation of 1-(3-aminopropyl)-3-[2-[4-(trifluoromethoxy)-phenyl] pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride was carried out in the same manner as that described for the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride using 4-trifluoromethoxy-benzene boronic acid. Purification afforded the title carboxylic acid as a brown solid. 3% yield over 2 steps. LCMS showed a single peak with m/z 407 (M+H). ES^+ HR MS calculated for M+H 407.1326, observed 407.1358.

EXAMPLE 75

[000314] This example illustrates the production of 2-[2-(4-methoxyphenyl)-pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000315] This compound was prepared as part of a parallel library. A reaction tube was charged with ethyl 1-(3-aminopropyl)-3-[2-(4-

methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride (250 mg, 0.55 mmol), 20 mL ammonium hydroxide, and 10 mL ethanol. The reaction mixture was stirred at room temperature for 18 hours. The mixture was then concentrated *in vacuo*, washed with water, filtered, and vacuum dried to afford 150 mg (81%) of the title lactam as a tan solid. LCMS showed a single peak with m/z 335 (M+H). ^{1}H nmr (DMSO-d_6 + TFA/300 MHz) δ 8.78 (d, 1H), 8.68 (s, 1H), 8.43 (br s, 1H), 8.26 (d, 1H), 8.09 (d, 2H), 7.93 (s, 1H), 7.23 (d, 2H), 4.59 (m, 2H), 3.89 (s, 3H), 3.26 (m, 2H), 2.21 (m, 2H). ES$^+$ HR MS calculated for M+H 335.1503, observed 335.1490.

EXAMPLE 76

[000316] This example illustrates the production of 2-[2-[4-(dimethylamino)-phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate.

[000317] The preparation of 2-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate was carried out in a manner similar to that described for the preparation of 2-[2-(4-methoxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one, except that it was chromatographed on a Gilson reverse phase HPLC eluting with an acetonitrile/water gradient (5-70% CH_3CN over 15 minutes). The pure fractions were combined and concentrated to afford the title lactam as a yellow solid (44% yield). LCMS showed a single peak with m/z 348 (M+H). ^{1}H nmr (DMSO-d_6/300 MHz) δ 8.61 (d, 1H), 8.52 (s, 1H), 8.41 (br s, 1H), 8.03 ((d, 2H), 7.98 (d, 1H), 7.84 (s, 1H), 6.89 (d, 2H), 4.57 (t, 2H), 3.25 (m, 2H), 3.05 (s, 6H), 2.21 (m, 2H). mp=223.0-226.7°C ES$^+$ HR MS calculated for M+H 348.1819, observed 348.1790.

EXAMPLE 77

[000318] This example illustrates the production of 2-[2-[3-(hydroxymethyl)-phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate.

[000319] The preparation of 2-[2-[3-(hydroxymethyl)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate was carried out in a manner similar to that described for the preparation of 2-[2-(4-methoxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one, except that it was chromatographed on a Gilson reverse phase HPLC eluting with an acetonitrile/water gradient (5-70% CH_3CN over 15 minutes). The pure fractions were combined and concentrated to afford the lactam as a white solid (26% yield). LCMS showed a single peak with m/z 335 (M+H). ^1H nmr (DMSO-d_6/300 MHz) δ 8.71 (d, 1H), 8.40 (s, 1H), 8.35 (br s, 1H), 8.11 (s, 1H), 8.03 (d, 1H), 7.86 (d, 1H), 7.63 (s, 1H), 7.53-7.41 (m, 2H), 4.61 (s, 2H), 4.54 (t, 2H), 3.24 (m, 2H), 2.19 (m, 2H). ES^+ HR MS calculated for M+H 335.1503, observed 335.1520.

EXAMPLE 78

[000320] This example illustrates the production of 2-[2-[4-(trifluoromethoxy)-phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000321] The preparation of 2-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one was carried out in a manner similar to that described for the preparation of 2-[2-(4-methoxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one. The mixture was then concentrated *in vacuo*, washed with water, filtered, and vacuum dried to afford the title lactam as an off-white solid (85%). LCMS showed a single peak with m/z 389 (M+H). ^1H nmr (DMSO-d_6/300 MHz) δ 8.70 (d, 1H), 8.40 (s, 1H), 8.33 (m, 3H), 7.82 (d, 1H), 7.62 (s, 1H), 7.49 (d, 2H), 4.53 (m, 2H), 3.24 (m, 2H), 2.19 (m, 2H). ES^+ HR MS calculated for M+H 389.1220, observed 389.1225.

EXAMPLE 79

[000322] This example illustrates the production of 2-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one.

[000323] Step 1. The preparation of ethyl 1-(3-aminopropyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride was carried out in a manner similar to that described for the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride, step 1 using 4-hydroxymethylphenyl boronic acid. Upon completion of the reaction, ethyl acetate and water were added. The layers were separated, and the organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated. The resulting residue was treated with excess 4 N HCl/dioxane for 15 minutes at room temperature. The reaction mixture was then chromatographed on a Gilson reverse phase HPLC eluting with an acetonitrile/water gradient (5-70% CH_3CN over 15 minutes). The pure fractions were combined, taken up in MeOH, and treated with 4 N HCl/dioxane to afford the HCl salt of the amine ester as a red solid (19 % yield). LCMS showed one major peak with *m/z* 381 (M+H).

[000324] Step 2. The preparation of 2-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one was carried out in a manner similar to that described for the preparation of 2-[2-(4-methoxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one. The product mixture was concentrated and filtered to afford the lactam as a tan solid (44% yield). LCMS showed a single peak with m/z 335 (M+H). ES^+ HR MS calculated for M+H 335.1503, observed 335.1520.

EXAMPLE 80

[000325] This example illustrates the production of ethyl 1-(3-aminopropyl)-3-[2-(4 hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride.

[000326] The preparation of ethyl 1-(3-aminopropyl)-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride was carried out in a manner similar to that described for the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic

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acid hydrochloride, step 1 using 4-hydroxyphenyl boronic acid THP ether. Upon completion of the reaction in step 1, ethyl acetate and water were added. The layers were separated, and the organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated. The residue was treated with excess 4 N HCl/dioxane for 15 minutes. The mixture was concentrated, triturated with ether, and filtered to afford the title amine ester as a tan solid (95% yield). LCMS showed one major peak with m/z 367 (M+H). mp = 241.6-244.4 °C.

EXAMPLE 81

[000327] This example illustrates the production of 1-(3-aminopropyl)-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride.

[000328] The preparation of 1-(3-aminopropyl)-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride was carried out in a manner similar to that described for the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)-pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride, step 2. The title carboxylic acid was obtained as an off-white solid (51% yield).). LCMS showed a single peak with m/z 339 (M+H). ES^+ HR MS calculated for M+H 339.1452, observed 339.1455.

EXAMPLE 82

[000329] This example illustrates the production of 2-[2-(4-hydroxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate.

[000330] The preparation of 2-[2-(4-hydroxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate was carried out in a manner similar to that described for the preparation of 2-[2-(4-methoxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one. Upon completion of the reaction, the product mixture was concentrated, washed with water, and filtered. The mixture was then chromatographed on a Gilson reverse phase HPLC eluting with

an acetonitrile/water gradient (5-70% CH_3CN over 15 minutes). The pure fractions were combined and concentrated to afford the title compound as an off-white solid (41% yield). LCMS showed a single peak with m/z 321 (M+H). ^1H NMR (DMSO-d_6/300 MHz) δ 8.72 (d, 1H), 8.63 (s, 1H), 8.42 (br s, 1H), 8.22 (d, 1H), 8.02 (d, 2H), 7.81 (s, 1H), 7.03 (d, 2H), 4.57 (m, 2H), 3.25 (m, 2H), 2.20 (m, 2H). ES^+ HR MS calculated for M+H 321.1346, observed 321.1368.

EXAMPLE 83

[000331] This examples illustrates the production of 1-{3-[[2-(4-bromophenyl)ethyl]-amino}propyl)-3-{2-[(E)-2-phenylvinyl]pyridin-4-yl}-1H-pyrazole-5-carboxylic acid trifluoroacetate.

[000332] Step 1. Preparation of ethyl 1-{3-[[2-(4-bromophenyl)ethyl](tert-butoxycarbonyl)-amino]propyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate. A single neck roundbottom flask was charged with ethyl 3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (1.0 g, 4.0 mmol) and 30 mL dimethyl formamide under N_2. The solution was cooled to –40 °C in a dry ice/acetonitrile bath. A 1 M solution of lithium *t*-butoxide in THF (4.8 mL, 4.8 mmol) was added dropwise over 5 minutes. The reaction was stirred for 1 hour at –40 °C. A solution of 3-[[2-(4-bromophenyl)ethyl](tert-butoxycarbonyl)amino]propyl methanesulfonate (2.1 g, 4.8 mmol) in 10 mL dimethylformamide was added dropwise over 5 minutes. The resulting reaction mixture was stirred for 1 hour at –40 °C, and then stirred for 18 hours at room temperature. The mixture was then concentrated, and the residue taken up in diethyl ether. The solid impurities were filtered off, and washed with diethyl ether.The filtrate was concentrated to a brown oil. LCMS showed a mixture of the ethyl ester and hydrolyzed carboxylic acid. This product mixture was taken on to the next step without further purification.

[000333] Step 2. The preparation of ethyl 1-(3-[[2-(4-bromophenyl)ethyl]amino}- propyl)-3-{2-[(E)-2-phenylvinyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate. hydrochloride was carried out in a manner similar

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to that described in example 2, step 1, using 2-phenylvinyl boronic acid. Upon completion of the reaction, ethyl acetate and water were added. The layers were separated, and the organic layer was washed with water, dried over magnesium sulfated, filtered and concentrated. The residue was treated with excess 4N HCl/dioxane for 30 minutes. The mixture was concentrated, washed with ether, and filtered to afford the ethyl ester as a brown solid (29% yield over 2 steps). LCMS showed one major peak with m/z 559 (M+H). ES^+ HR MS calculated for M+H 559.1703, observed 559.1679.

[000334] Step 3. The preparation of 1-(3-{[2-(4-bromophenyl)ethyl]amino}propyl)-3-[2-[(E)-2-phenylvinyl]pyridin-4-yl}-1H-pyrazole-5-carboxylic acid trifluoroacetate was carried out in a manner similar to that described for the production of 1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride, step 2. Upon completion of the reaction, the mixture was concentrated. The residue was then chromatographed on a Gilson reverse phase HPLC eluting with an acetonitrile/water gradient (5-70% CH_3CN over 15 minutes). The pure fractions were combined and concentrated to afford the title compound as an off-white solid (30% yield). LCMS showed a single peak with m/z 531 (M+H). ES^+ HR MS calculated for M+H 531.1390, observed 531.1411.

EXAMPLE 84

[000335] This examples illustrates the production of ethyl 1-[2-[(tert-butoxy-carbonyl)amino]ethyl]-3-[2-(4-[[tert-butyl(dimethyl)silyl]oxy}phenyl)-pyridin-4-yl]-1H-pyrazole-5-carboxylate.

[000336] Ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate (5.0 g, 0.013 mol), 4-(t-butyldimethylsilyloxy)phenyl boronic acid (6.4 g, 0.025 mol), sodium carbonate (2.7 g, 0.025 mol), water (12.5 mL), and [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium (II)complex with dichloromethane (1:1) (1.0 g, 0.0013 mol) in toluene (100 mL) were

refluxed for 4 hours. Contents were allowed to cool and partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a pad of silica gel, eluting with 25% EtOAc/hexanes to give a light amber oil. The oil crystallized under hexanes and was filtered to give the desired product as a white solid, 3.77 g (51% yield). FABHRMS m/z 567.2983 (M+H, $C_{30}H_{43}N_4O_5Si$ requires 567.2997). ^1H NMR ($CDCl_3$/300 MHz): 8.70 (s, 1H); 8.12 (s, 1H); 7.97 (d, 2H); 7.60 (s, 1H); 7.29 (d, 1H); 6.95 (d, 2H); 4.97 (br, 1H); 4.77 (t, 2H); 4.40 (q, 2H); 3.63 (br, 2H); 1.40 (t, 3H); 1.38 (s, 9H); 1.00 (s, 9H); 0.25 (s, 6H).

[000337] Anal. Calculated for $C_{30}H_{42}N_4O_5Si$: C, 63.58; H, 7.47; N, 9.89. Found: C, 63.51; H, 7.58; N, 9.73.

EXAMPLE 85

[000338] This example illustrates the preparation of ethyl 1-(2-aminoethyl)-3-[2-(4-[[tert-butyl(dimethyl)silyl]oxy}phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride.

[000339] Ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-[2-(4-[[tert-butyl(dimethyl)-silyl]oxy}phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate (1.0 g, 0.0018 mol) and 4N HCl in dioxane were mixed for 2 hours and filtered to give the desired product as a white solid, 875 mg (90% yield). FABHRMS m/z 467.2450 (M+H, $C_{25}H_{35}N_4O_3Si$ requires 467.2473). ^1H NMR (DMSO-d_6 + TFA /300 MHz): 8.80 (d, 1H); 8.75 (s, 1H); 8.35 (d, 1H); 8.22 (br, 3H); 8.20-8.10 (m, 3H); 7.13 (d, 2H); 4.90 (t, 2H); 4.40 (q, 2H); 3.40 (q, 2H); 1.39 (t, 3H); 0.95 (s, 9H); 0.23 (s, 6H).

[000340] Anal. Calculated for $C_{25}H_{34}N_4O_3Si$ (2 HCl, 1.1 H_2O): C, 53.68; H, 6.88; N, 10.02. Found: C, 53.34; H, 6.98; N, 10.18.

EXAMPLE 86

[000341] This example illustrates the production of 2-[2-(4-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000342] Ethyl 1-(2-aminoethyl)-3-[2-(4-[[tert-butyl(dimethyl)silyl]oxy}phenyl) pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride (770 mg, 0.0014 mol), conc ammonium hydroxide (2 mL)

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and methanol (20 mL) were stirred overnight. Contents were concentrated *in vacuo* and the residue was slurried in water and filtered to give the desired product as a white solid, 373 mg, (87% yield). FABHRMS m/z 307.1222 (M+H, $C_{17}H_{15}N_4O_2$ requires 307.1190). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.75 (d, 1H); 8.63 (s, 1H); 8.40 (s, 1H); 8.21 (d, 1H); 8.00-7.95 (m, 3H); 7.00 (d, 2H); 4.43 (t, 2H); 3.65 (br, 2H).

[000343] Anal. Calculated for $C_{17}H_{14}N_4O_2$ (1.3 H_2O): C, 61.92; H, 5.07; N, 16.99. Found: C, 61.79; H, 5.11; N, 16.85.

EXAMPLE 87

[000344] This example illustrates the production of 2-[2-[4-(2-morpholin-4-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000345] 2-[2-(4-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (500 mg, 0.0016 mol), 4-(2-chloroethyl)morpholine hydrochloride (372 mg (0.002 mol) and potassium carbonate (600 mg, 0.004 mol) were heated in DMF (20 mL) at 80°C for 3 hours. Contents were allowed to cool, diluted with water (50 mL), cooled to 0°C and filtered to give the desired product as a white solid, 515 mg (77% yield). FABHRMS m/z 420.2004 (M+H, $C_{23}H_{26}N_5O_3$ requires 420.2030). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.81 (d, 1H); 8.66 (s, 1H); 8.43 (s, 1H); 8.23 (d, 1H); 8.15 (d, 2H); 7.94 (s, 1H); 7.28 (d, 2H); 4.55-4.40 (m, 4H); 4.05-3.95 (m, 2H); 3.80-3.50 (m, 8H); 3.30-3.18 (m, 2H).

[000346] Anal. Calculated for $C_{23}H_{25}N_5O_3$ (0.8 H_2O): C, 63.60; H, 5.96; N, 16.25. Found: C, 63.67; H, 6.18; N, 16.14.

EXAMPLE 88

[000347] This example illustrates the production of 2-(2-[4-[2-(dimethylamino)ethoxy]-phenyl]pyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000348] 2-(2-[4-[2-(dimethylamino)ethoxy]phenyl]pyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one was prepared according to the procedure of 2-[2-[4-(2-morpholin-4-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one to give the desired product as a

white solid (72% yield). FABHRMS m/z 378.1901 (M+H, $C_{21}H_{24}N_5O_2$ requires 378.1925). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 9.80 (br, 1H); 8.80 (d, 1H); 8.70 (s, 1H); 8.42 (s, 1H); 8.28 (d of d, 1H); 8.12 (d, 2H); 7.96 (s, 1H); 7.28 (d, 2H); 4.50-4.40 (m, 4H); 3.70 (br, 2H); 3.60 (br, 2H); 2.90 (s, 6H). Anal. Calculated for $C_{21}H_{23}N_5O_2$ (0.6 H_2O): C, 64.91; H, 6.15; N, 18.03. Found: C, 64.97; H, 6.28; N, 18.04.

EXAMPLE 89

[000349] This example illustrates the production of Ethyl 1-(2-aminoethyl)-3-{2-[3-(benzyloxy)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate dihydrochloride.

[000350] Ethyl 1-[2-[(tert-butoxycarbonyl)amino]ethyl]-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate and 3-benzyloxyboronic acid were reacted according to the procedure described for the preparation of ethyl 1-[2-[(tert-butoxycarbonyl)-amino]ethyl]-3-[2-(4-[[tert-butyl(dimethyl)silyl]oxy}phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate, to give ethyl 1-(2-t-butoxycarbonylaminoethyl)-3-{2-[3-(benzyloxy-phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate as a light amber oil. Ethyl 1-(2-t-butoxycarbonylaminoethyl)-3-{2-[3-(benzyloxy)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate and 4N HCl in dioxane were stirred 3 hours and filtered to give the desired product as a pale yellow solid, 8.0 g (81% yield). FABHRMS m/z 443.2053 (M+H, $C_{26}H_{27}N_4O_3$ requires 443.2078). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.88 (d, 1H); 8.80 (s, 1H); 8.10 (s, 1H); 8.05 (br, 3H); 7.78 (s, 1H); 7.65 (d, 1H); 7.55 (t, 1H); 7.45 (d, 1H); 7.40-7.30 (m, 6H); 5.21 (s, 2H); 4.85 (t, 2H); 4.35 (q, 2H); 3.40 (q, 2H); 1.35 (t, 3H).

[000351] Anal. Calculated for $C_{26}H_{26}N_4O_3$ (3HCl, H_2O): C, 54.80; H, 5.48; N, 9.83. Found: C, 55.01; H, 5.84; N, 10.75.

EXAMPLE 90

[000352] This example illustrates the production of 2-[2-[3-(benzyloxy)phenyl]-pyridin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

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[000353] 2-[2-[3-(benzyloxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one was prepared according to the procedure for the preparation of 2-[2-(4-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one, using ethyl 1-(2-aminoethyl)-3-[2-[3-(benzyloxy)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride, to give the desired product as a white solid (63% yield). FABHRMS m/z 397.1634 (M+H, $C_{24}H_{21}N_4O_2$ requires 397.1659). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.81 (d, 1H); 8.62 (s, 1H); 8.40 (s, 1H); 8.21 (d, 1H); 7.92 (s, 1H); 7.80 (s, 1H); 7.70 (d, 1H); 7.63 – 7.25 (m, 6H); 5. 23 (s, 2H); 4.51-4.40 (m, 2H); 3.78-3.60 (m, 2H). *Anal.* Calculated for $C_{24}H_{20}N_4O_2$ (H_2O): C, 69.55; H, 5.35; N, 13.52. Found: C, 69.65; H, 5.11; N, 14.50.

EXAMPLE 91

[000354] This example illustrates the production of ethyl 1-(2-aminoethyl)-3-[2-(3-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride.

[000355] Ethyl 1-(2-t-butoxycarbonylaminoethyl)-3-[2-[3-(benzyloxy)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate (9.1 g, 0.017 mol), prepared as for ethyl 1-(2-aminoethyl)-3-[2-[3-(benzyloxy)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride and 10% palladium/carbon (2.0 g) in ethanol (150 mL) were shaken at 55 psi H_2 on a Parr hydrogenator for three and a half days. Contents were filtered through clay and the filtrate was concentrated *in vacuo* leaving a pale yellow solid (6.4 g). The solid and 4N HCl in dioxane were stirred overnight and filtered to give the desired product as a white solid, 6.0 g (83% yield). HRMS calculated for (M + H) 353.1608, found 353.1630. ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.86 (d, 1H); 8.77 (s, 1H); 8.40 (d, 1H); 8.20 (br s, 3H); 8.12 (s, 1H); 7.59-7.40 (m, 3H); 7.09 (d, 1H); 4.90 (t, 2H), 4.39 (q, 2H); 3.40 (q, 2H); 1.35 (t, 3H).

EXAMPLE 92

[000356] This example illustrates the production of 2-[2-[3-(2-morpholin-4-ylethoxy)-phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

[000357] 2-[2-[3-(2-morpholin-4-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo-[1,5-a]pyrazin-4(5H)-one was prepared according to the procedure for 2-[2-[4-(2-morpholin-4-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one, using 2-[2-(3-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one and chloroethylmorpholine hydrochloride to give the desired as a white solid (55% yield). FABHRMS m/z 420.1996 (M+H, $C_{23}H_{25}N_5O_3$ requires 420.2030). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.85 (d, 1H); 8.61 (s, 1H); 8.40 (s, 1H); 8.21 (d, 1H); 7.89 (s, 1H); 7.78 (s, 2H);7.59 (t, 1H); 7.28 (d, 1H); 4.58-4.40 (m, 4H); 4.08-3.91 (m 2H); 3.84-3.48 (m, 8H); 3.45-3.13 (m, 2H).

[000358] Anal. Calculated for $C_{23}H_{25}N_5O_3$ (0.7 H_2O): C, 63.93; H, 6.16; N, 16.21. Found: C, 63.93; H, 5.96; N, 16.42.

EXAMPLE 93

[000359] This example illustrates the preparation of 2-(2-Chloropyridin-4-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one.

[000360] Step 1. Preparation of 2-Chloro-4-hydrazinopyridine hydrochloride. A solution of 4-amino-2-chloropyridine (1.0 g, 7.78 mmol) in 20% sulfuric acid (20 mL) was cooled to 0 °C and treated with a solution of sodium nitrite (564 mg, 8.17 mmol) in water (3 mL) at a rate such that the reaction temperature did not exceed 10 °C. After 15 minutes, the solution was added to a 0°C suspension of tin(II) chloride in 20% sulfuric acid (20 mL). The frothy suspension was stirred for 15 minutes at 0 °C and then warmed to room temperature over 15 minutes. The mixture was poured into 100 mL of ice water and made basic with concentrated ammonium hydroxide. The product was extracted with diethyl ether and ethyl acetate repeatedly. The organic layers were dried (sodium sulfate) and concentrated to give crude 2-chloro-4-hydrazinopyridine as a yellow solid (830 mg, 5.78 mmol). The solid was dissolved in tetrahydrofuran (5 mL) and diluted with diethyl ether (15 mL). The solution was treated with 1 N HCl in diethyl ether (5.8 mL, 5.8 mmol). The white precipitate was filtered and washed with ether to give 2-chloro-4-hydrazinopyridine

hydrochloride as a white solid (995 mg, 5.53 mmol, 71% yield). LC-MS (ES+) MH^+ = 144. ^1H NMR (300 MHz, DMSO-d_6) δ 10.0-9.40 (br s, 4H), 8.07 (d, J = 6.1, 1H), 6.95 (d, J = 1.9, 1H), 6.86 (dd, J = 5.8, 2.0, 1H).

[000361] Step 2. Preparation of Piperidine-2,4-dione 4-[(2-chloropyridin-4-yl)hydrazone]. A mixture of 2-chloro-4-hydrazinopyridine hydrochloride (961 mg, 5.33 mmol), piperdiene-2.4-dione (Example 1, step 3) (604 mg, 5.33 mmol) and ethanol (20 mL) was refluxed overnight. The reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL), and filtered. The precipitate was washed with 50% ethanol/diethyl ether and dried to give piperidine-2,4-dione 4-[(2-chloropyridin-4-yl)hydrazone] as an off-white solid (940 mg, 3.94 mmol, 74% yield). LC-MS (ES+) MH^+ = 239.

[000362] Step 3. Preparation of 2-(2-Chloropyridin-4-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one.

[000363] A mixture of piperidine-2,4-dione 4-[(2-chloropyridin-4-yl)hydrazone] (863 mg, 3.62 mmol) in dimethylformamide dimethyl acetal (16 mL) was refluxed for 1 hour. The solvent was removed under reduced pressure. The residue was suspended in ethanol/diethyl ether and filtered. The precipitate was washed with 50% ethanol/diethyl ether to give 2-(2-chloropyridin-4-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one as an off-white solid (378 mg, 1.52 mmol, 42% yield). The mother liquor was concentrated and purified by flash chromatography (0→10% methanol/ethyl acetate). The resultant oil was triturated with methanol/ether to give another 58 mg (0.23 mmol, 6%) of 2-(2-chloropyridin-4-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one. ^1H NMR (300 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.47 (d, J = 5.7, 1H), 8.04 (d, J = 1.6, 1H), 7.94 (dd, J = 5.5, 1.8, 1H), 7.71 (br s, 1H), 3.44 (td, J = 6.5, 2.6, 2H), 2.89 (t, J = 6.6, 2H). HRMS calculated for $C_{11}H_{10}ClN_4O$ (MH^+) 249.0538, found 249.0545.

EXAMPLE 94

[000364] This example illustrates the preparation of 2-(2-quinolin-3-ylpyridin-4-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one bis(trifluoroacetate).

[000365] The title compound was prepared from 2-(2-chloropyridin-4-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one (Example 508) and 3-quinolinylboronic acid by the procedure described for Example 2. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (d, J = 2.2, 1H), 9.38 (s, 1H), 9.26 (d, J = 2.0, 1H), 8.82 (d, J = 5.4, 1H), 8.71 (d, J = 1.6, 1H), 8.16 (d, J = 7.7, 1H), 8.12 (d, J = 8.3, 1H), 7.96 (dd, J = 5.6, 2.0, 1H), 7.87 (td, J = 7.7, 1.3, 1H), 7.76-7.68 (m, 2H), 3.48 (td, J = 6.6, 2.4, 2H), 2.95 (t, J = 6.6, 2H). HRMS *calculated* for $C_{20}H_{16}N_5O$ (MH^+) 342.1349, found 342.1334.

[000366] The following examples were made by the same method.

Example No.	Compound Name(s)	Calculated (m+H)	Found (m+H)
95	2-[2-(2-fluorophenyl)pyridin-4-yl]-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one trifluoroacetate	309.1146	309.119
96	2-(2-phenylpyridin-4-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one trifluoroacetate	291.124	291.1252

EXAMPLE 97

[000367] This example illustrates the preparation of 2-{2-[(E)-2-(4-morpholin-4-ylphenyl)vinyl]pyridin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate.

[000368] mp 290°C (decomposition); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (d, *J* = 6.5 Hz, 1H), 8.39 (2 x s, 2H), 7.97-7.83 (m, 2H), 7.70 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 16.2 Hz, 1H), 7.03 (d, *J* = 16.2 Hz, 2H), 4.50-4.38 (m, 2H), 3.80-3.60 (m, 6H), 3.28-3.19 (m, 4H); *m/z* 402 $[M+H]^+$.

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EXAMPLE 98

[000369] This example illustrates that MK2 knock-out mice (MK2 (-/-)) are resistant to the formation of K/BN serum-induced arthritis and that compounds that inhibit MK-2 should be effective for the prevention and treatment of TNFα-mediated diseases or disorders.

A strain of mice has been reported that develops symptoms similar to human rheumatoid arthritis. The mice were designated K/BxN mice. See, Wipke, B. T. and P. M. Allen, *J. of Immunology, 167*:1601 - 1608 (2001). Serum from the mice can be injected into host animals to provoke a typical RA response. The progression of the RA symptoms in the mice is measured by measuring paw thickness as a function of time.

[000370] In the present example, host mice having normal MK-2 production (MK2 (+/+)) were genetically altered by disabling the gene encoding MK-2 to produce mice having no capability of endogenous synthesis of active MK-2 (MK2 (-/-)). Normal host mice (MK2 (+/+)) and MK-2 knock-out mice (MK2 (-/-), were separated into four groups with each group containing both male and female mice. All groups of mice were treated similarly, except that one group (Normal), composed of MK2 (+/+) mice that served as the control group, was not injected with serum from K/BxN mice, while the other three groups were injected with K/BxN serum at day 0. The other three groups of mice were MK2 (+/+), MK2 (-/-), and Anti-TNF. The Anti-TNF group was composed of MK2 (+/+) mice which were also injected at day) with anti-TNF antibody. The paw thickness of all mice was measured immediately after the injections on day 0, and then on each successive day thereafter for 7 days.

[000371] Figure 1 is a graph that shows paw thickness as a function of time from day 0 to day 7 for MK2 (+/+) and MK2 (-/-) mice, which have received serum injection. It can be seen that paw thickness increased significantly for MK2(+/+) mice, whereas there was substantially no increase in paw thickness for MK2 knock-out mice. This indicated the requirement for a functioning MK2 regulatory system to the inflammatory response caused by the serum challenge. When anti-TNF antibody was

administered to the MK2 (+/+) mice along with the serum injection, the swelling response was significantly reduced. This can be seen in Figure 2, which is a bar chart showing paw thickness at seven days after injection for normal mice, MK2 (+/+) mice receiving serum, MK2 (-/-) mice receiving serum, and MK2 (+/+) mice receiving serum and anti-TNF antibody.

[000372] This data shows that the MK2 knock-out mice show no arthritic response to a serum challenge, whereas MK2 (+/+) mice show a normal response. Treatment of MK2 (+/+) mice that receive a serum challenge with anti-TNF antibody reduces the response back to near-normal levels. This illustrates the utility of the MK2 regulatory system as a potential control point for the modulation of TNF production, and indicates that such regulation could serve as a treatment for inflammation -- such as that caused by arthritis, for example. It further shows that MK2 inhibition can have a beneficial effect on inflammation, and indicates that administration of an MK2 inhibitor can be an effective method of preventing or treating TNF modulated diseases or disorders.

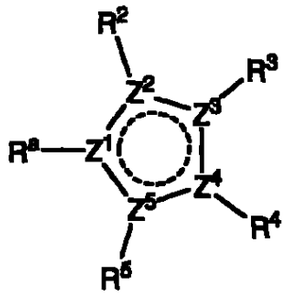
[000373] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000374] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000375] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A compound having the structure:

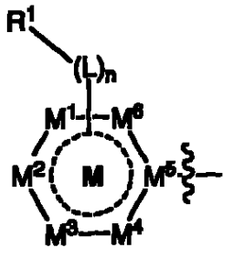


wherein:

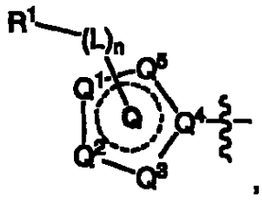
Z^2 and Z^3 are nitrogen, Z^1, Z^4 and Z^5 are carbon, and join with Z^2 and Z^3 to form a pyrazole ring, or optionally, Z^4 and Z^5 are nitrogen, Z^1, Z^2 and Z^3 are carbon and join with Z^4 and Z^5 to form a pyrazole ring;

R^a is selected from:

1)

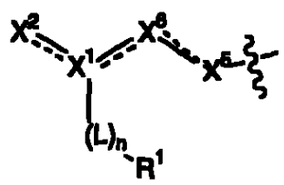


2)



, and

3)



where dashed lines indicate optional single or double bonds;

when R^a is ring M and ring M is aromatic, M^1 is carbon and is substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon and nitrogen and is unsubstituted or substituted with $(L)_nR^1$;

when ring M is partially saturated, M^1 is carbon and is mono- or di-substituted with $(L)_nR^1$, M^5 is carbon, and each of M^2, M^3, M^4 and M^6 is independently selected from carbon, nitrogen, oxygen and sulfur, and when M^2, M^3, M^4, or M^6 is oxygen or sulfur, it is unsubstituted, and when M^2, M^3, M^4 or M^6 is carbon or nitrogen, it is optionally unsubstituted; or mono- or di-substituted with $(L)_nR^1$;

when R^a is ring Q and ring Q is aromatic, Q^1 is selected from carbon and nitrogen, and when Q^1 is carbon, it is substituted with $(L)_nR^1$, and when Q^1 is nitrogen, it is unsubstituted, Q^4 is selected from nitrogen and carbon, and each of Q^2, Q^3 and Q^5 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

optionally when ring Q is aromatic, Q^1 is carbon and is substituted with $(L)_nR^1$, Q^4 is carbon, and one of Q^2, Q^3 and Q^5 is optionally oxygen or sulfur, and the remainder of Q^2, Q^3 and Q^5 are independently selected from nitrogen and carbon, and if carbon, are substituted with $(L)_nR^1$;

when ring Q is partially saturated, Q^1 is selected from carbon and nitrogen, and if carbon, it is mono- or di-substituted with $(L)_nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$, Q^4 is selected from carbon and nitrogen, but only one of Q^1 and Q^4 can be nitrogen, each of Q^2, Q^3 and Q^5 is independently selected from carbon, nitrogen, oxygen and sulfur, and if oxygen or sulfur, it is unsubstituted, and if carbon, it is

mono- or di-substituted with $(L)_nR^1$, and if nitrogen, it is unsubstituted or substituted with $(L)_nR^1$;

when R^a is structure 3, it is fully conjugated, X^2 is selected from oxygen or nitrogen substituted with $(L)_nR^1$, X^1 is carbon and is substituted with $(L)_nR^1$, and each of X^5 and X^6 is independently selected from nitrogen and carbon, and if carbon, it is substituted with $(L)_nR^1$;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-R^{11}, C_2-C_8 alkenyl-R^{11}, C_2-C_8 alkynyl-R^{11}, C_1-C_8 alkyl-$(R^{11})_2$, C_2-C_8 alkenyl-$(R^{11})_2$, CSR^{11}, amino, $CONHR^{11}$, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NR^8R^9, $(C_1$-$C_4)$alkyl-$N(R^7)$-$N(R^8)(R^9)$, $(C_1$-$C_4)$alkyl$C(R^{11})$=N-$N(R^8)(R^9)$, $(C_1$-$C_4)$alkyl-N=$N(R^7)$, $(C_1$-$C_4)$alkyl-$N(R^7)$-N=$C(R^8)$, nitro, cyano, CO_2R^{11}, O-R^{10}, C_1-C_4 alkyl-OR^{10}, COR^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_8 alkyl-COR^{11}, C_1-C_8 alkyl-SR^{10}, C_1-C_8 alkyl-SOR^{11}, C_1-C_8 alkyl-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7, R^8 and R^9 are each independently selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_4 alkyl-R^{11}, C_1-C_8 alkyl-NHR^{13}, C_1-C_8 alkyl-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alkyl-OR^{15}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, $C(O)R^{17}$, $C(S)R^{17}$, $CONHR^{16}$, $C(S)NHR^{16}$, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SR^{16}, SOR^{17}, SO_2R^{17}, C_1-C_8 alkyl-CO_2R^{15}, C_1-C_8 alkyl-$C(S)OR^{15}$, C_1-C_8 alkyl-$C(O)SR^{15}$, C_1-C_8 alkyl-COR^{17}, C_1-C_8 alkyl-$C(S)R^{17}$, C_1-C_8 alkyl-$CONHR^{16}$, C_1-C_8 alkyl-$C(S)NHR^{16}$, C_1-C_8 alkyl-$CON(R^{16})_2$, C_1-C_8 alkyl-$C(S)N(R^{16})_2$, C_1-C_8 alkyl-SR^{15}, C_1-C_8 alkyl-SOR^{17}, C_1-C_8 alkyl-SO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl,

alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{10} is selected from -H, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-NHR^{13}, C_1-C_8 alkyl-$NR^{13}R^{14}$, C_1-C_4 alkyl-OR^{15}, CSR^{11}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, COR^{17}, $C(S)R^{17}$, $CONHR^{16}$, C_1-C_4 alkyl-R^{11}, C_1-C_4 alkyl-NH_2R^{13}, $C(S)NHR^{16}$, O-R^{15}, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SOR^{17}, SO_2R^{17}, C_1-C_8 alkyl-CO_2R^{15}, C_1-C_8 alkyl-$C(S)OR^{15}$, C_1-C_8 alkyl-$C(O)SR^{15}$, C_1-C_8 alkyl-COR^{17}, C_1-C_8 alkyl-$C(S)R^{17}$, C_1-C_8 alkyl-$CONHR^{16}$, C_1-C_8 alkyl-$C(S)NHR^{16}$, C_1-C_8 alkyl-$CON(R^{16})_2$, $Si(R^{13})_2R^{17}$, C_1-C_8 alkyl-$C(S)N(R^{16})_2$, C_1-C_8 alkyl-SR^{15}, C_1-C_8 alkyl-SOR^{17}, C_1-C_8 alkyl-SO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, amino, NHR^{13}, $NR^{13}R^{14}$, $N{=}NR^{13}$, C_1-C_8 alkyl-NHR^{13}, C_1-C_8 alkyl-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alkyl-OR^{15}, SR^{15}, COR^{13}, CO_2R^{17}, C_1-C_8 alkyl-CO_2R^{15}, C_1-C_8 alkyl-$C(S)OR^{15}$, C_1-C_8 alkyl-$C(O)SR^{15}$, C_1-C_8 alkyl-COR^{17}, C_1-C_8 alkyl-$C(S)R^{17}$, C_1-C_8 alkyl-$CONHR^{16}$, C_1-C_8 alkyl-$C(S)NHR^{16}$, C_1-C_8 alkyl-$CON(R^{16})_2$, C_1-C_8 alkyl-$C(S)N(R^{16})_2$, C_1-C_8 alkyl-SR^{15}, C_1-C_8 alkyl-SOR^{17}, C_1-C_8 alkyl-SO_2R^{17}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, OH, oxo, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{11}, C_2-C_{10} alkenyl-R^{11}, C_2-C_{10} alkynyl-R^{11}, C_1-C_{10}

alkyl-$(R^{11})_2$, C_2-C_{10} alkenyl-$(R^{11})_2$, CSR^{11}, hydroxyl C_1-C_6 alkyl-R^{11}, amino C_1-C_4 alkyl-R^7, amino, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_{10} alkyl-NHR^7, C_1-C_{10} alkyl-NR^8R^9, (C_1-C_{10})alkyl-$N(R^7)$-$N(R^8)(R^9)$, (C_1-C_{10})alkyl$C(R^{11})$=N-$N(R^8)(R^9)$, (C_1-C_{10})alkyl-N=$N(R^7)$, (C_1-C_{10})alkyl-$N(R^7)$-N=$C(R^8)$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{10}, C_1-C_{10} alkyl-OR^{10}, COR^{11}, CO_2R^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_{10} alkyl-COR^{11}, C_1-C_{10} alkyl-SR^{10}, C_1-C_{10} alkyl-SOR^{11}, C_1-C_{10} alkyl-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{13};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_4 alkyl-R^{23}, C_1-C_6 alkyl-NHR^{19}, C_1-C_6 alkyl-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alkyl-OR^{21}, CO_2R^{21}, COR^{21}, $C(S)OR^{21}$, $C(O)SR^{21}$, $C(O)R^{23}$, $C(S)R^{23}$, $CONHR^{22}$, $C(S)NHR^{22}$, $CON(R^{22})_2$, $C(S)N(R^{22})_2$, SR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_6 alkyl-CO_2R^{21}, C_1-C_6 alkyl-$C(S)OR^{21}$, C_1-C_6 alkyl-$C(O)SR^{21}$, C_1-C_6 alkyl-COR^{23}, C_1-C_6 alkyl-$C(S)R^{23}$, C_1-C_6 alkyl-$CONHR^{22}$, C_1-C_6 alkyl-$C(S)NHR^{22}$, C_1-C_6 alkyl-$CON(R^{22})_2$, C_1-C_6 alkyl-$C(S)N(R^{22})_2$, C_1-C_6 alkyl-SR^{21}, C_1-C_6 alkyl-SOR^{23}, C_1-C_6 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{15} and R^{16} are independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl-NHR^{19}, C_1-C_6 alkyl-$NR^{19}R^{20}$, C_1-C_4

alkyl-OR^{21}, CSR^{11}, CO_2R^{22}, COR^{23}, $CONHR^{22}$, $CON(R^{22})_2$, SOR^{23}, SO_2R^{23}, C_1-C_6 alkyl-CO_2R^{22}, C_1-C_6 alkyl-COR^{23}, C_1-C_6 alkyl-$CONHR^{22}$, C_1-C_6 alkyl-$CON(R^{22})_2$, C_1-C_6 alkyl-SR^{21}, C_1-C_6 alkyl-SOR^{23}, C_1-C_6 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl-R^{19}, C_1-C_6 alkyl-R^{19}, C_2-C_6 alkynyl, amino, NHR^{19}, $NR^{19}R^{20}$, C_1-C_6 alkyl-NHR^{19}, C_1-C_6 alkyl-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alkyl-OR^{21}, SR^{21}, C_1-C_6 alkyl-CO_2R^{21}, C_1-C_6 alkyl-$C(S)OR^{21}$, C_1-C_6 alkyl-$C(O)SR^{21}$, C_1-C_6 alkyl-COR^{23}, C_1-C_6 alkyl-$C(S)R^{23}$, C_1-C_6 alkyl-$CONHR^{22}$, C_1-C_6 alkyl-$C(S)NHR^{22}$, C_1-C_6 alkyl-$CON(R^{22})_2$, C_1-C_6 alkyl-$C(S)N(R^{22})_2$, C_1-C_6 alkyl-SR^{21}, C_1-C_6 alkyl-SOR^{23}, C_1-C_6 alkyl-SO_2R^{23}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{23}, C_2-C_{10} alkenyl-R^{23}, C_2-C_{10} alkynyl-R^{23}, C_1-C_{10} alkyl-$(R^{23})_2$, C_2-C_{10} alkenyl-$(R^{23})_2$, CSR^{23}, amino, NHR^{19}, $NR^{20}R^{20}$, $N(R^{19})$-$N(R^{20})(R^{20})$, $C(R^{23})$=N-$N(R^{20})(R^{20})$, N=$N(R^{19})$, $N(R^{19})$-N=$C(R^{20})$, $C(R^{23})$=N-$O(R^{21})$, ON=$C(R^{23})$, C_1-C_{10} alkyl-NHR^{19}, C_1-C_{10} alkyl-$NR^{20}R^{20}$, (C_1-C_{10})alkyl-$N(R^{19})$-$N(R^{20})(R^{20})$, (C_1-C_{10})alkyl$C(R^{23})$=N-$N(R^{20})(R^{20})$, (C_1-C_{10})alkyl-N=$N(R^{19})$, (C_1-C_{10})alkyl-$N(R^{19})$-N=$C(R^{20})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{21}, C_1-C_{10} alkyl-OR^{21}, COR^{23}, CO_2R^{23}, SR^{21}, SSR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_{10} alkyl-COR^{23}, C_1-C_{10}

alkyl-SR^{21}, C_1-C_{10} alkyl-SOR^{23}, C_1-C_{10} alkyl-SO_2R^{23}, halo, $Si(R^{23})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_4 alkyl-R^{29}, C_1-C_8 alkyl-NHR^{25}, C_1-C_8 alkyl-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alkyl-OR^{27}, CO_2R^{27}, $C(S)OR^{27}$, $C(O)SR^{27}$, $C(O)R^{29}$, $C(S)R^{29}$, $CONHR^{29}$, $C(S)NHR^{29}$, $CON(R^{29})_2$, $C(S)N(R^{29})_2$, SR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_8 alkyl-CO_2R^{27}, C_1-C_8 alkyl-$C(S)OR^{27}$, C_1-C_8 alkyl-$C(O)SR^{27}$, C_1-C_8 alkyl-COR^{29}, C_1-C_8 alkyl-$C(S)R^{29}$, C_1-C_8 alkyl-$CONHR^{29}$, C_1-C_8 alkyl-$C(S)NHR^{29}$, C_1-C_8 alkyl-$CON(R^{29})_2$, C_1-C_8 alkyl-$C(S)N(R^{29})_2$, C_1-C_8 alkyl-SR^{27}, C_1-C_8 alkyl-SOR^{29}, C_1-C_8 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are independently selected from -H, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkyl-NHR^{25}, C_1-C_8 alkyl-$NR^{25}R^{26}$, C_1-C_4 alkyl-OR^{27}, CSR^{11}, CO_2R^{29}, COR^{29}, $CONHR^{29}$, $CON(R^{29})_2$, SOR^{29}, SO_2R^{29}, C_1-C_8 alkyl-CO_2R^{29}, C_1-C_8 alkyl-COR^{29}, C_1-C_8 alkyl-$CONHR^{29}$, C_1-C_8 alkyl-$CON(R^{29})_2$, C_1-C_8 alkyl-SR^{27}, C_1-C_8 alkyl-SOR^{29}, C_1-C_8 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic

cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{23} is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl-R^{25}, C_1-C_6 alkyl-R^{25}, C2-C_6 alkynyl, amino, NHR^{25}, $NR^{25}R^{26}$, C_1-C_6 alkyl-NHR^{25}, C_1-C_6 alkyl-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alkyl-OR^{27}, SR^{27}, C_1-C_6 alkyl-CO_2R^{27}, C_1-C_6 alkyl-$C(S)OR^{27}$, C_1-C_6 alkyl-$C(O)SR^{27}$, C_1-C_6 alkyl-COR^{29}, C_1-C_6 alkyl-$C(S)R^{29}$, C_1-C_6 alkyl-$CONHR^{26}$, C_1-C_6 alkyl-$C(S)NHR^{26}$, C_1-C_6 alkyl-$CON(R^{25})_2$, C_1-C_6 alkyl-$C(S)N(R^{25})_2$, C_1-C_6 alkyl-SR^{27}, C_1-C_6 alkyl-SOR^{29}, C_1-C_6 alkyl-SO_2R^{29}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{24} is selected from -H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{29}, C_2-C_{10} alkenyl-R^{29}, C_2-C_{10} alkynyl-R^{29}, C_1-C_{10} alkyl-$(R^{29})_2$, C_2-C_{10} alkenyl-$(R^{29})_2$, CSR^{29}, amino, NHR^{25}, $NR^{25}R^{26}$, $N(R^{25})$-$N(R^{26})(R^{29})$, $C(R^{29})$=N-$N(R^{26})(R^{29})$, N=$N(R^{25})$, $N(R^{25})$-N=$C(R^{29})$, $C(R^{29})$=N-$O(R^{27})$, ON=$C(R^{29})$, C_1-C_{10} alkyl-NHR^{25}, C_1-C_{10} alkyl-$NR^{26}R^{26}$, (C_1-C_{10})alkyl-$N(R^{25})$-$N(R^{26})(R^{29})$, (C_1-C_{10})alkylC(R^{29})=N-$N(R^{26})(R^{29})$, (C_1-C_{10})alkyl-N=$N(R^{25})$, (C_1-C_{10})alkyl-$N(R^{25})$-N=$C(R^{29})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{27}, C_1-C_{10} alkyl-OR^{27}, CO_2R^{29}, COR^{29}, SR^{27}, SSR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_{10} alkyl-COR^{29}, C_1-C_{10} alkyl-SR^{27}, C_1-C_{10} alkyl-SOR^{29}, C_1-C_{10} alkyl-SO_2R^{29}, halo, $Si(R^{29})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{30};

R^{25} and R^{29} are each independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_4 alkyl-R^{35}, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alkyl-OR^{33}, CO_2R^{33}, $C(S)OR^{33}$, $C(O)SR^{33}$, $C(O)R^{35}$, $C(S)R^{35}$, $CONHR^{34}$, $C(S)NHR^{34}$, $CON(R^{34})_2$, $C(S)N(R^{34})_2$, SR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_6 alkyl-CO_2R^{33}, C_1-C_6 alkyl-$C(S)OR^{33}$, C_1-C_6 alkyl-$C(O)SR^{33}$, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$C(S)R^{35}$, C1-C_6 alkyl-$CONHR^{34}$, C1-C_6 alkyl-$C(S)NHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-$C(S)N(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{27} and R^{28} are independently selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, C_1-C_4 alkyl-OR^{33}, CSR^{11}, CO_2R^{34}, COR^{35}, $CONHR^{34}$, $CON(R^{34})_2$, SOR^{35}, SO_2R^{35}, C_1-C_6 alkyl-CO_2R^{34}, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$CONHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-SOR^{35}, C_1-C_6 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{29} is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkenyl-R^{31}, C_1-C_6 alkyl-R^{31}, C_2-C_6 alkynyl, amino, NHR^{31}, $NR^{31}R^{32}$, C_1-C_6 alkyl-NHR^{31}, C_1-C_6 alkyl-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alkyl-OR^{33}, SR^{33}, C_1-C_6 alkyl-CO_2R^{33}, C_1-C_6 alkyl-$C(S)OR^{33}$, C_1-C_6 alkyl-$C(O)SR^{33}$, C_1-C_6 alkyl-COR^{35}, C_1-C_6 alkyl-$C(S)R^{35}$, C_1-C_6 alkyl-$CONHR^{34}$, C_1-C_6 alkyl-$C(S)NHR^{34}$, C_1-C_6 alkyl-$CON(R^{34})_2$, C_1-C_6 alkyl-$C(S)N(R^{34})_2$, C_1-C_6 alkyl-SR^{33}, C_1-C_6 alkyl-

SOR^{35}, C_1-C_8 alkyl-SO_2R^{35}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{30} is selected from -H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkyl-R^{35}, C_2-C_{10} alkenyl-R^{35}, C_2-C_{10} alkynyl-R^{35}, C_1-C_{10} alkyl-$(R^{35})_2$, C_2-C_{10} alkenyl-$(R^{35})_2$, CSR^{35}, $N{=}NR^{31}$, amino, NHR^{31}, $NR^{32}R^{32}$, $N(R^{31})$-$N(R^{32})(R^{32})$, $C(R^{35}){=}N$-$N(R^{32})(R^{32})$, $N{=}N(R^{31})$, $N(R^{31})$-$N{=}C(R^{32})$, $C(R^{35}){=}N$-$O(R^{33})$, $ON{=}C(R^{35})$, C_1-C_{10} alkyl-NHR^{31}, C_1-C_{10} alkyl-$NR^{32}R^{32}$, (C_1-C_{10})alkyl-$N(R^{31})$-$N(R^{32})(R^{32})$, (C_1-C_{10})alkyl$C(R^{35}){=}N$-$N(R^{32})(R^{32})$, (C_1-C_{10})alkyl-$N{=}N(R^{31})$, (C_1-C_{10})alkyl-$N(R^{31})$-$N{=}C(R^{32})$, SCN, NCS, C_1-C_{10} alkyl SCN, C_1-C_{10} alkyl NCS, nitro, cyano, O-R^{33}, C_1-C_{10} alkyl-OR^{33}, COR^{35}, SR^{33}, SSR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_{10} alkyl-COR^{35}, C_1-C_{10} alkyl-SR^{33}, C_1-C_{10} alkyl-SOR^{35}, C_1-C_{10} alkyl-SO_2R^{35}, halo, $Si(R^{35})_3$, halo C_1-C_{10} alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{31}, R^{32}, R^{33} and R^{34} are each independently selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{35} is selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, OH, alkoxy, amino, alkylamino, dialkylamino, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{36};

R^{36} is selected from –H, alkyl, alkenyl, alkynyl, aminoalkyl, OH, alkoxy, amino, nitro, cyano, halo, alkylamino, dialkylamino, hydroxyalkyl, alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heterocyclylalkyl, and heteroarylalkyl;

R^2, R^3, R^4, R^5, R^{37} and R^{38} are each independently absent, or selected from an R^1 group;

n is 0; and

R^3 and R^4 optionally join to form a ring of 5, 6, 7, or 8 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

2. The compound according to claim 1, wherein when Z^2 and Z^3 are both nitrogen, R^4 is other than pyrrole, or optionally when Z^4 and Z^5 are both nitrogen and R^a is ring Q, Q^2 is other than nitrogen.

3. The compound according to claim 1, wherein R^a is selected from an M-ring and a Q-ring.

4. The compound according to claim 1, wherein R^a is an M-ring.

5. The compound according to claim 4, wherein ring M is an aromatic pyridine or pyrimidine ring, wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$.

6. The compound according to claim 1, wherein R^6 is an M-ring, wherein ring M is an aromatic pyridine or pyrimidine ring, wherein M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$, M^5 is carbon, M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$.

7. The compound according to claim 1, wherein:

R^6 is an M-ring that is an aromatic pyridine or pyrimidine ring;

M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon;

M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$; and

R^3 and R^4 optionally join to form a ring of 5, 6, 7, or 8 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

8. The compound according to claim 1, wherein:

R^6 is an M-ring that is an aromatic pyridine or pyrimidine;

M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon;

M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$; and

R^3 and R^4 optionally join to form a ring of 6 or 7 atoms, where the atoms in the ring are independently selected from Z^3, Z^4, C=O, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

9. The compound according to claim 1, wherein:

R^6 is an M-ring that is an aromatic pyridine or pyrimidine;

M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon;

M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$; and R^3 and R^4 optionally join to form a ring of 6 atoms, where the atoms in the ring are

Independently selected from Z^3, Z^4, C=O, C that is mono or di-substituted with an R^1 group, and N that is unsubstituted or substituted with an R^1 group.

10. The compound according to claim 1, wherein:

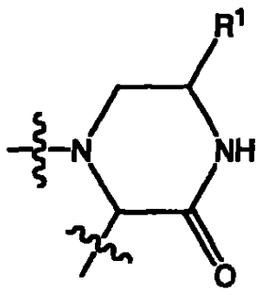
R^a is an M-ring that is an aromatic pyridine or pyrimidine ring;

M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$;

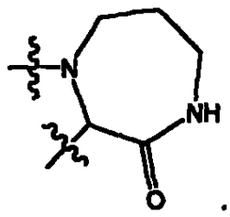
M^5 is carbon;

M^2 and M^6 are independently selected from carbon and nitrogen and if carbon, the carbon is substituted with $(L)_nR^1$; and

R^3 and R^4 optionally join to form a ring that is selected from:



, and



.

11. The compound according to claim 1, wherein:

R^a is an M-ring that is an aromatic pyridine;

M^1, M^3, M^4 and M^6 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon; and

M^2 is nitrogen.

12. The compound according to claim 1, wherein:

R^a is an M-ring that is an aromatic pyrimidine:

M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon; and

M^2 and M^6 are nitrogen.

13. The compound according to claim 1, wherein:

R^6 is an M-ring that is an aromatic pyridine:

M^1, M^3, M^4 and M^6 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon;

M^2 is nitrogen;

R^1 is selected from -H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl-R^{11}, C_1-C_8 alkoxy-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl-R^7, halo C_1-C_4 alkyl, C_1-C_8 alkyl-NHR^7, carbonitrile, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_8 alkyl, NR^8R^9-C_1-C_8 alkyl, nitro, cyano, O-R^{10}, C_1-C_4 alkyl-OR^{10}, C_1-C_8 alkyl-COR^{11}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7 and R^8 are each independently selected from -H, C_1-C_8 alkyl, C_1-C_4 alkyl-R^{11}, C_1-C_8 alkyl-$N(R^{13})_2$, CO_2R^{18}, COR^{17}, aryl, and arylalkyl, wherein aryl and arylalkyl, are optionally subetituted with one or more of the groups defined by R^{18};

R^9 and R^{10} are each independently selected from -H, hydroxyl, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{17}, C_1-C_8 alkyl-NH_2R^{13}, CO_2R^{18}, COR^{17}, C_1-C_8 alkyl-CO_2R^{18}, C_1-C_8 alkyl-$CONH$-R^{18}, C_1-C_8 alkyl-$CON(R^{18})_2$, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkoxy, halo C_1-C_4 alkyl, $Si(R^{13})_2R^{17}$, aryl, heteroaryl, heterocyclyl, arylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxyl, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, wherein heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, hydroxyl, oxo, C_1-C_8 alkyl, hydroxyl C_1-C_8 alkyl-R^{11}, C_1-C_{10} alkoxy, amino, amino C_1-C_4 alkyl-R^7, NHR^7, $N(R^7)_2$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NHR^8R^8, C_1-C_8 alkyl-$N(R^8)_2$, C_1-C_8 alkyl-R^{11}, C_1-C_8 alkyl-$CO_2R^7R^{11}$, C_1-C_8 alkoxy-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_8 alkyl-SR^{10}, halo, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, COR^{23}, and aryl;

R^{15} and R^{16} are each independently selected from -H, aryl, arylalkyl, wherein aryl, arylalkyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{19}, NHR^{19}, aryl, heteroarylalkyl, and heterocyclylalkyl, wherein aryl is optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, hydroxyl, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, amino, amino C_1-C_8 alkyl, $N(R^{19})_2$, C_1-C_8 alkyl-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_8 alkyl, heteroaryl, heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are each independently selected from –H and C_1-C_8 alkyl;

R^{23} is selected from –H and C_1-C_8 alkyl;

R^{24} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, CO_2R^{29}, halo, and halo C_1-C_4 alkyl;

R^{29} is selected from -H, and C_1-C_6 alkyl;

R^{30} is selected from -H, aryl, heteroaryl, heterocyclyl, alkylaryl, arylalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{36};

R^{36} is selected from –H and halo; and

R^2, R^3, R^4, R^{37} and R^{38} are each independently selected from an R^1 group.

14. The compound according to claim 1, wherein:

R^6 is an M-ring that is an aromatic pyrimidine;

M^1, M^3 and M^4 are carbon and are substituted with $(L)_nR^1$;

M^5 is carbon;

M^2 and M^6 are nitrogen;

R^1 is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl-R^{11}, C_1-C_6 alkoxy-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl-R^7, halo C_1-C_4 alkyl, C_1-C_6 alkyl-NHR^7, carbonitrile, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_6 alkyl, NR^8R^9-C_1-C_6 alkyl, nitro, cyano, O-R^{10}, C_1-C_4 alkyl-OR^{10}, C_1-C_6 alkyl-COR^{11}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, or C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{12};

R^7 and R^8, are each independently selected from -H, C_1-C_6 alkyl, C_1-C_4 alkyl-R^{11}, C_1-C_6 alkyl-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, aryl, and arylalkyl, wherein aryl and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^9 and R^{10} are each independently selected from -H, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkyl-R^{17}, C_1-C_6 alkyl-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alkyl-CO_2R^{16}, C_1-C_6 alkyl-CONH-R^{16}, C_1-C_6 alkyl-$CON(R^{16})_2$, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkoxy, halo C_1-C_4 alkyl, $Si(R^{13})_2R^{17}$, aryl, heteroaryl, heterocyclyl, arylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein

aryl, heteroaryl, heterocyclyl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{11} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxyl, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, wherein heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, are optionally substituted with one or more of the groups defined by R^{18};

R^{12} is selected from -H, hydroxyl, oxo, C_1-C_8 alkyl, hydroxyl C_1-C_8 alkyl-R^{11}, C_1-C_{10} alkoxy, amino, amino C_1-C_4 alkyl-R^7, NHR^7, $N(R^7)_2$, C_1-C_8 alkyl-NHR^7, C_1-C_8 alkyl-NHR^8R^9, C_1-C_8 alkyl-$N(R^8)_2$, C_1-C_8 alkyl-R^{11}, C_1-C_8 alkyl-$CO_2R^7R^{11}$, C_1-C_8 alkoxy-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_8 alkyl-SR^{10}, halo, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclylalkyl, and C_1-C_{10} mono- and bicyclic cycloalkyl are optionally substituted with one or more of the groups defined by R^{18};

R^{13} and R^{14} are each independently selected from -H, oxo, C_1-C_8 alkyl, COR^{23}, and aryl;

R^{15} and R^{16} are each independently selected from -H, aryl, arylalkyl, wherein aryl, arylalkyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{17} is selected from -H, C_1-C_8 alkyl, C_1-C_8 alkyl-R^{19}, NHR^{19}, aryl, heteroarylalkyl, and heterocyclylalkyl, wherein aryl is optionally substituted with one or more of the groups defined by R^{24};

R^{18} is selected from -H, oxo, hydroxyl, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, amino, amino C_1-C_8 alkyl, $N(R^{19})_2$, C_1-C_8 alkyl-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{24};

R^{19} and R^{20} are each independently selected from -H, C_1-C_6 alkyl, heteroaryl, heterocyclyl, wherein aryl, heteroaryl, and heterocyclyl, are optionally substituted with one or more of the groups defined by R^{30};

R^{21} and R^{22} are each independently selected from –H and C_1-C_6 alkyl;

R^{23} is selected from –H and C_1-C_6 alkyl;

R^{24} is selected from -H, C_1-C_6 alkyl, C_1-C_6 alkoxy, CO_2R^{29}, halo, and halo C_1-C_4 alkyl;

R^{29} is selected from -H, and C_1-C_6 alkyl;

R^{30} is selected from -H, aryl, heteroaryl, heterocyclyl, alkylaryl, arylalkyl, wherein aryl, heteroaryl, heterocyclyl, alkylaryl, and arylalkyl, are optionally substituted with one or more of the groups defined by R^{39};

R^{39} is selected from –H and halo; and

R^2, R^3, R^4, R^{37} and R^{38} are each independently selected from an R^1 group.

15. An MK-2 inhibiting compound that is listed in Table I or Table II.

16. The compound according to claim 15, wherein the compound is selected from the group consisting of:

1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid trifluoroacetate,

1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride,

6-(aminomethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one,

1-(2-aminoethyl)-3-[2-[(E)-2-phenylethenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate,

1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride,

6-(hydroxymethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one, and

1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid dihydrochloride, and mixtures thereof.

17. A method of inhibiting MK-2, the method comprising contacting MK-2 with at least one compound having the structure described in claim 1.

18. A method of inhibiting MK-2, the method comprising contacting MK-2 with at least one compound that is selected from the compounds described in claim 15.

19. A method of preventing or treating a TNFα mediated disease or disorder in a subject, the method comprising administering to the subject an effective amount of an MK-2 inhibiting compound having the structure described in claim 1.

20. The method according to claim 19, wherein the subject is one that is in need of such prevention or treatment.

21. The method according to claim 19, wherein the subject is a mammal.

22. The method according to claim 19, wherein the subject is a human.

23. The method according to claim 19, wherein the TNFα mediated disease or disorder is one that is selected from the group consisting of wherein the TNFα mediated disease or disorder is one that is selected from the group consisting of connective tissue and joint disorders, neoplasia disorders, cardiovascular disorders, otic disorders, ophthalmic disorders, respiratory disorders, gastrointestinal disorders, angiogenesis-related disorders, immunological disorders, allergic disorders, nutritional disorders, infectious diseases and disorders, endocrine disorders, metabolic disorders, neurological and neurodegenerative disorders, psychiatric disorders, hepatic and biliary disorders, musculoskeletal disorders, genitourinary disorders, gynecologic and obstetric disorders, injury and trauma disorders, surgical disorders, dental and oral disorders, sexual dysfunction disorders, dermatologic disorders, hematological disorders, and poisoning disorders.

24. The method according to claim 19, wherein the TNFα mediated disease or disorder is selected from the group consisting of: arthritis, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, cancer, colorectal cancer, herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, ophthalmic diseases, retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue, pulmonary inflammation, viral infections, cystic fibrosis, central nervous system disorders, cortical dementias, and Alzheimer's disease.

25. A method of preventing or treating a TNFα mediated disease or disorder in a subject, the method comprising administering to the subject at least one MK-2 inhibiting compound that is selected from the group consisting of the compounds described in claim 15.

26. A therapeutic composition comprising a compound having the structure described in claim 1.

27. A therapeutic composition comprising at least one MK-2 inhibitory compound that is described in claim 15.

28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one MK-2 inhibitory compound having the structure described in claim 1.

29. The pharmaceutical composition according to claim 28, wherein the MK-2 inhibitory compound has an IC_{50} for MK-2 of not over 0.1 mM.

30. A kit comprising a dosage form that includes a therapeutically effective amount of at least one MK-2 inhibitory compound having a structure described in claim 1.

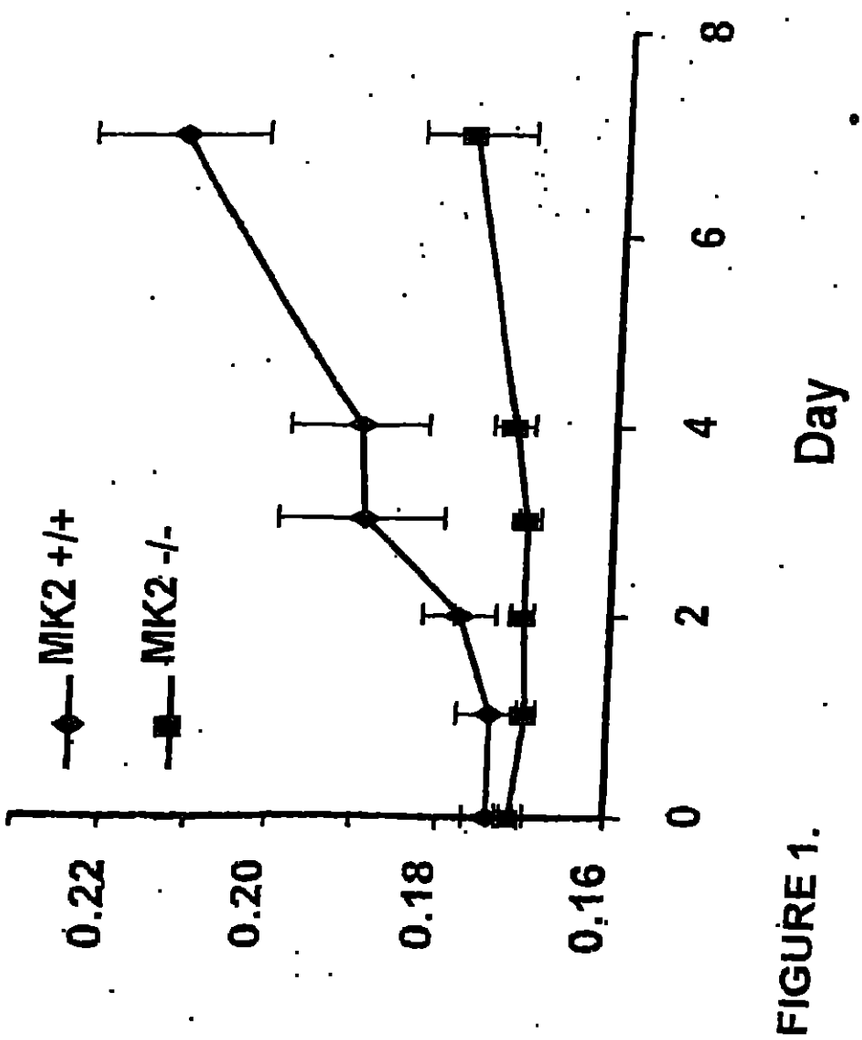


FIGURE 1.

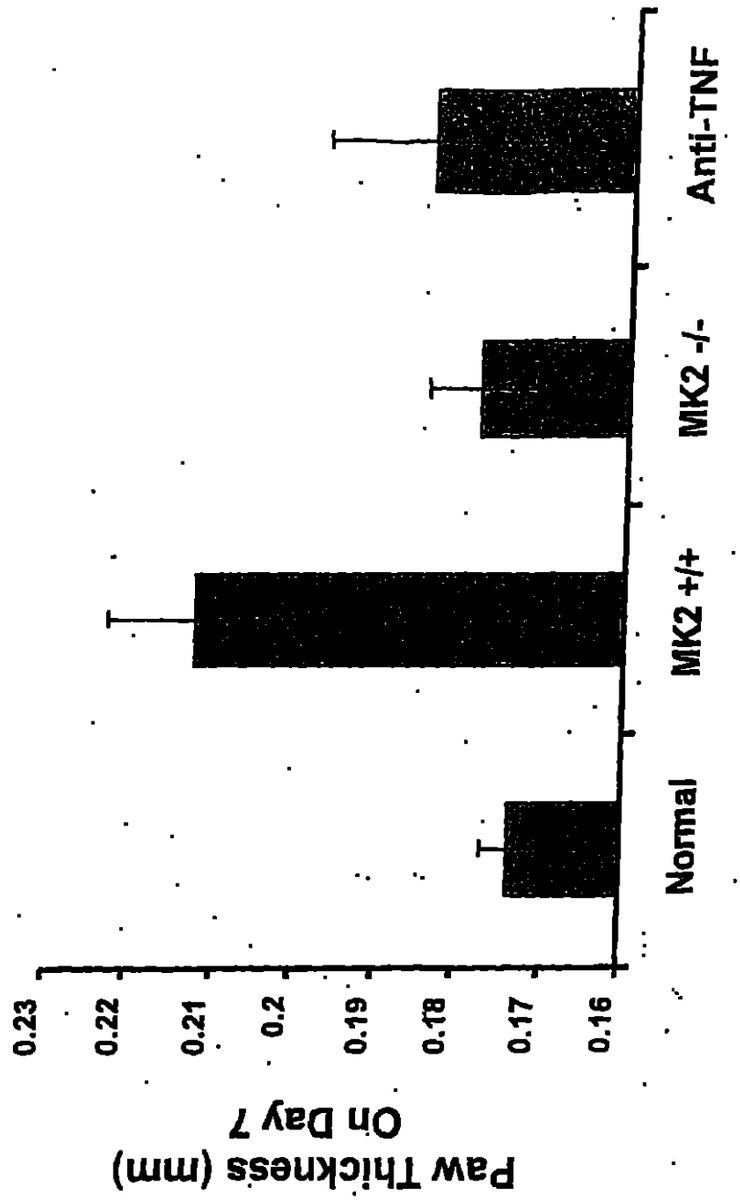

Paw Thickness (mm)
On Day 7
0.23
0.22
0.21
0.2
0.19
0.18
0.17
0.16
Normal
MK2 +/+
MK2 -/-
Anti-TNF

FIGURE 2.

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AP:97382

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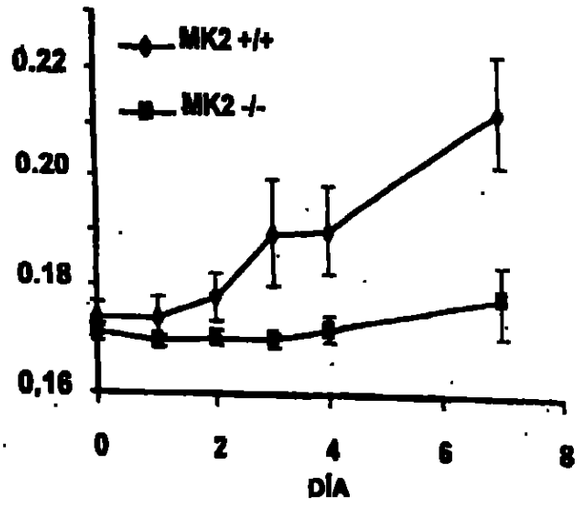
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[Continúa en la página siguiente]

(54) Título: COMPUESTOS DE PIRAZOL ACÍCLICO PARA LA INHIBICIÓN DE PROTEÍNA CINASA-2 ACTIVADA POR PROTEÍNA CINASA ACTIVADA POR MITÓGENOS



(57) Extracto: Se describen compuestos que inhiben la proteína cinasa-2 activada por proteína cinasa activada por mitógenos (MK-2). Se describen métodos de preparar tales compuestos, así como un método de usarlos para la inhibición de MK-2, y para la prevención o tratamiento de una enfermedad o trastorno que es mediado por TNFα, donde el método incluye administrar al individuo un compuesto inhibidor de MK-2 de la presente invención. Se describen asimismo composiciones farmacéuticas y estuches que contienen los presentes compuestos inhibidores de MK-2.

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COMPUESTOS DE PIRAZOL ACÍCLICO PARA LA INHIBICIÓN DE PROTEÍNA CINASA-2 ACTIVADA POR PROTEÍNA CINASA ACTIVADA POR MITÓGENOS

REFERENCIA CRUZADA A PATENTES Y SOLICITUDES DE PATENTE RELACIONADAS

[0001] Esta solicitud se relaciona con las reivindicaciones y el beneficio de la Solicitud de Patente Provisional de los Estados Unidos Serie No. 60/434,962, presentado el 20 de diciembre de 2002, que se incorpora aquí por referencia en su totalidad.

ANTECEDENTES DE LA INVENCIÓN

(1) Campo de la Invención:

[0002] La presente invención se refiere a ciertos compuestos cíclicos y heterocíclicos que inhiben la proteína cinasa-2 activada por proteína cinasa activada por mitógenos (MAPKAP cinasa-2, o MK-2), así como a métodos de emplear tales compuestos para inhibir MK-2 y para la prevención y tratamiento de enfermedades o trastornos mediados por TNFα en individuos que necesitan de tal prevención y/o tratamiento.

(2) Descripción del Arte Relacionado:

[0003] Proteína cinasas activadas por mitógenos (MAPKs) son miembros de vías de transducción de señales conservadas que activan factores de transcripción, factores de traslado y otras moléculas diana en respuesta a una variedad de señales extracelulares. Las MAPKs se activan por fosforilación en un motivo de fosforilación dual con la secuencia Thr-X-Tyr por cinasas de proteína cinasa activada por mitógenos (MAPKKs). En eucariotas superiores, el papel fisiológico de la señalización MAPK se ha correlacionado con acontecimientos celulares tales como proliferación, oncogénesis, desarrollo y diferenciación. En consecuencia, la capacidad de regular la transducción de señales mediante estas vías podría llevar al

desarrollo de tratamientos y terapias preventivas para enfermedades humanas asociadas con la señalización de MAPK, tales como enfermedades inflamatorias, enfermedades autoinmunitarias y cáncer. 142

[0004] En las células de mamíferos, se han descrito tres vías MAPK paralelas. La vía mejor caracterizada lleva a la activación de la cinasa regulada por señales extracelulares (ERK). Menos entendidas son las vías de transducción de señales que llevan a la activación de la cinasa N-terminal cJun (JNK) y la p38 MAPK. Véase, *por ejemplo*, Davis, *Trends Biochem. Sci. 19*:470-473 (1994); Cano, *et al., Trends Biochem. Sci. 20*:117-122 (1995).

[0005] La vía p38 MAPK se activa potencialmente por una amplia variedad de tensiones y agresiones celulares. Estas tensiones y agresiones celulares incluyen choque térmico, irradiación de UV, citocinas inflamatorias (tales como TNF y IL-1), tunicamicina, medicamentos quimioterapéuticos (*es decir*, cisplatino), anisomicina, sorbitol/hiperosmolaridad, irradiación gamma, arseniato de sodio, e isquemia. Véase, Ono, K., *et al, Cellular Signalling 12*, 1-13 (2000). La activación de la vía p38 se encuentra involucrada en (1) la producción de citocinas proinflamatorias, tales como TNF-α; (2) inducción de enzimas, tales como Cox-2; (3) expresión de una enzima intracelular, tal como iNOS, que juega un papel importante en la regulación de la oxidación; (4) inducción de proteínas adherentes, tales como VCAM-1 y muchas otras moléculas relacionadas con la inflamación. Más aún, la vía p38 funciona como regulador en la proliferación y diferenciación de células del sistema inmunitario. Véase, Ono, K., *et al., Id.* en 7.

[0006] La cinasa p38 es una cinasa corriente arriba de la proteína cinasa-2 activada por proteína cinasa activada por mitógenos (MAPKAP cinasa-2 o MK-2). (Véase, Freshney, N. W., *et al., J. Cell, 78*: 1039-1049 (1994)). La MK-2 es una proteína que parece ser predominantemente regulada por p38 en las células. En efecto, la MK-2 fue el primer sustrato de p38α en identificarse. Por ejemplo, la fosforilación *in vitro* de MK-2 por p38α activa MK-2. Los sustratos sobre los que actúa MK-2, a su vez, incluyen la

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proteína 27 de choque térmico 27, la proteína 1 específica de linfocitos 1 (LAP1), proteína de fijación a elementos de respuesta cAMP (CREB), ATF1, factor de respuesta al (SRF), y tirosina hidroxilasa. El sustrato de MK-2 que mejor se ha caracterizado es la proteína 27 de choque térmico pequeño 27 (hsp27).

[0007] El papel de la vía p38 en enfermedades relacionadas con inflamación se ha estudiado en varios modelos animales. Se ha demostrado que el compuesto piridinil imidazol SB203580 es un inhibidor específico de p38 *in vivo*, y se ha demostrado además que inhibe la activación de MK-2, (Véase, Rouse, J., *et al, Cell, 78*: 1027-1037 (1994); Cuenda, A., *et al, Biochem. J., 333*:11-15 (1998)), así como un homólogo de cinasa MAP denominado cinasa reactivadora (RK). (Véase, Cuenda, A., *et al., FEBS Lett., 364(2)*: 229 - 233 (1995)). La inhibición de p38 por SB203580 puede disminuir la mortalidad en un modelo murino de choque inducido por endotoxinas e inhibir el desarrollo de artritis de ratón inducida por colágeno y artritis coadyuvante de rata. Véase, *por ejemplo*, Badger, A. M., *et al., J. Pharmacol Exp. Ther., 279:*1453 -1461 (1996). Otro inhibidor p38 que se ha utilizado en un modelo animal que se cree que es más potente que SB203580 en su efecto inhibidor sobre p38 es SB 220025. Un reciente estudio animal ha demostrado que SB 220025 causó una disminución significativa, dependiente de la dosis, en la densidad vascular de granulomas en ratas de laboratorio. (Véase, Jackson, J. R., *et al, J. Pharmacol. Exp. Ther., 284*: 687 - 692 (1998)). Los resultados de estos estudios animales indicaron que p38, o los componentes de la vía p38, pueden ser dianas terapéuticas útiles para la prevención o tratamiento de la enfermedad inflamatoria.

[0008] Debido a su papel integral en la vía de señalización p38, se ha usado MK-2 como monitor para medir el nivel de activación en la vía. Debido a su localización corriente abajo en la vía, relativa a p38, MK-2 se ha medido como un método más conveniente, si bien indirecto, de evaluar la activación de p38. Sin embargo, hasta ahora, los esfuerzos investigativos que exploran estrategias terapéuticas asociadas con la modulación de esta

vía se han centrado principalmente en la inhibición de cinasa p38.

[0009] Varios compuestos que inhiben la actividad de cinasa p38 se han descrito en las Patentes de los Estados Unidos Nos. 6,046,208, 6,251,914, y 6,335,340. Se ha sugerido que estos compuestos son útiles para el tratamiento de enfermedad mediada por CSBP/RK/p38. Los esfuerzos comerciales para aplicar los inhibidores p38 se han centrado alrededor de dos inhibidores de p38, el inhibidor piridinilimidazol SKF 86002, y el inhibidor 2,4,5 triaril imidazol SB203580. Véase, Lee, J. C, *et al, Immunopharmacology 47,* 185-192 (2000).

Asimismo se han investigado compuestos que poseen una estructura similar como inhibidores potenciales de p38. En efecto, el papel de la cinasa p38 MSP en varios estados patológicos se ha elucidado por el uso de inhibidores.

[00010] Kotlyarov, A. *et al,* in *Nat Cell Biol., 1(2)*:94 - 97 (1999) introdujo una mutación tomada como diana en un gen MK-2 de ratón, que tuvo como resultado ratones con deficiencia de MK-2. Se demostró que los ratones que carecían de MK-2 poseían una mayor resistencia al estrés y sobrevivieron el choque endotóxico inducido por LPS mejor que los ratones MK-2^{+}. Los autores concluyeron que MK-2 fue un componente esencial en la respuesta inflamatoria que regula la biosíntesis de TNFα en un nivel pos-transcripcional. Más recientemente, Lehner, M.D., *et al*, in *J. Immunol., 168(9)*: 4667-4673 (2002), informó que ratones con deficiencia de MK-2 mostraron una creciente susceptibilidad a la infección con *Listeria monocytogenes*, y concluyeron que MK-2 tenía un papel esencial en la defensa del anfitrión contra las bacterias intracelulares, probablemente mediante la regulación de TNF la producción de gamma IFN requeridas para la activación de mecanismos efectores antibacterianos.

[00011] La localización de MK-2 en la vía señalizadora p38 en un punto que se encuentra corriente abajo de p38 ofrece el potencial de que MK-2 pudiera actuar como un punto focal para modular la vía sin afectar tantos sustratos como lo haría la regulación de una enzima más corriente arriba en la cascada de señalización – tal como cinasa MAP p38.

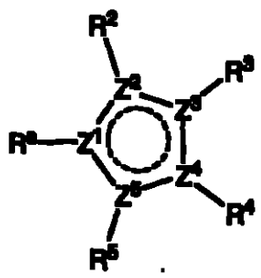
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[00012] por consiguiente, sería útil proporcionar compuestos y métodos que pudieran servir para modular la actividad de MK-2 – en particular, para actuar como inhibidores de la actividad MK-2. Tales compuestos y métodos serían útiles para la provisión de beneficios similares a inhibidores de cinasa MAP p38, beneficios que incluyen la prevención y tratamiento de enfermedades y trastornos que están mediados por TNFα. Será aún más útil proporcionar inhibidores de MK-2 que posean una potencia mejorada y efectos colaterales indeseados reducidos, en relación con los inhibidores de p38.

SUMARIO DE LA INVENCIÓN

[00013] Concretamente, por lo tanto, la presente invención de dirige a un compuesto novedoso con la estructura de fórmula I:

Formula I:



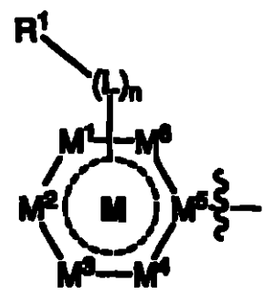
en donde:

Z^2 y Z^3 son nitrógeno, Z^1, Z^4 y Z^5 son carbono, y se juntan con Z^2 y Z^3 para formar un anillo pirazol, o de manera opcional, Z^4 y Z^5 son nitrógeno, Z^1, Z^2 y Z^3 son carbono y se juntan con Z^4 y Z^5 para formar un anillo pirazol;

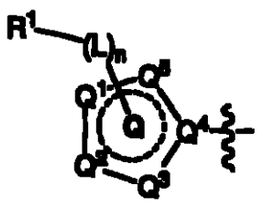
R^a se selecciona de:

1)

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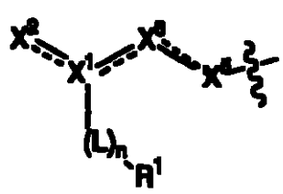


2)



, y

3)



donde las líneas discontinuas indican enlaces simples o dobles opcionales;

cuando R^a es anillo M y anillo M es aromático, M^1 es carbono y es sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono y nitrógeno y es no sustituido o sustituido con $(L)_nR^1$;

cuando anillo M es parcialmente saturado, M^1 es carbono y es mono- o di-sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y cuando M^2, M^3, M^4, o M^6 es oxígeno o azufre, es no sustituido, y cuando M^2, M^3, M^4 o M^6 es carbono o nitrógeno, es opcionalmente no sustituido; o mono- o di-sustituido con $(L)_nR^1$;

cuando R^a es anillo Q y anillo Q es aromático, Q^1 se selecciona de carbono y nitrógeno, y cuando Q^1 es carbono, se sustituye con $(L)_nR^1$, y cuando Q^1 es nitrógeno, es no sustituido, Q^4 se selecciona de nitrógeno y carbono, y cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de

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nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

opcionalmente, cuando anillo Q es aromático, Q^1 es carbono y es sustituido con $(L)_nR^1$, Q^4 es carbono, y uno de Q^2, Q^3 y Q^5 es opcionalmente oxígeno o azufre, y el resto de Q^2, Q^3 y Q^5 se seleccionan independientemente de nitrógeno y carbono, y si carbono, se sustituyen con $(L)_nR^1$;

cuando anillo Q es parcialmente saturado, Q^1 se selecciona de carbono y nitrógeno, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$, Q^4 se selecciona de carbono y nitrógeno, pero sólo uno de Q^1 y Q^4 puede ser nitrógeno, cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y si oxígeno o azufre, es no sustituido, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$;

cuando R^a es estructura 3, es completamente conjugado, X^2 se selecciona de oxígeno o nitrógeno sustituido con $(L)_nR^1$, X^1 es carbono y es sustituido con $(L)_nR^1$, y cada uno de X^5 y X^6 se selecciona independientemente de nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-R^{11}, C_2-C_6 alquenil-R^{11}, C_2-C_6 alquinil-R^{11}, C_1-C_6 alquil-$(R^{11})_2$, C_2-C_6 alquenil-$(R^{11})_2$, CSR^{11}, amino, $CONHR^{11}$, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NR^8R^9, $(C_1$-$C_4)$alquil-$N(R^7)$-$N(R^8)(R^9)$, $(C_1$-$C_4)$alquil$C(R^{11})$=N-$N(R^8)(R^9)$, $(C_1$-$C_4)$alquil-N=$N(R^7)$, $(C_1$-$C_4)$alquil-$N(R^7)$-N=$C(R^8)$, nitro, ciano, CO_2R^{11}, O-R^{10}, C_1-C_4 alquil-OR^{10}, COR^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_6 alquil-COR^{11}, C_1-C_6 alquil-SR^{10}, C_1-C_6 alquil-SOR^{11}, C_1-C_6 alquil-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo,

arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{12};

R^7, R^8 y R^9 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alquil-OR^{15}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, $C(O)R^{17}$, $C(S)R^{17}$, $CONHR^{16}$, $C(S)NHR^{16}$, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SR^{15}, SOR^{17}, SO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{10} se selecciona de -H, C_1-C_{10} alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, C_1-C_4 alquil-OR^{15}, CSR^{11}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, COR^{17}, $C(S)R^{17}$, $CONHR^{16}$, C_1-C_4 alquil-R^{11}, C_1-C_4 alquil-NH_2R^{13}, $C(S)NHR^{16}$, O-R^{15}, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SOR^{17}, SO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, $Si(R^{13})_2R^{17}$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de

manera opcional por uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_2-C_6 alquenilo, C_2-C_6 alquinilo, amino, NHR^{13}, $NR^{13}R^{14}$, $N=NR^{13}$, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alquil-OR^{15}, SR^{15}, COR^{13}, CO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, OH, oxo, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{11}, C_2-C_{10} alquenil-R^{11}, C_2-C_{10} alquinil-R^{11}, C_1-C_{10} alquil-$(R^{11})_2$, C_2-C_{10} alquenil-$(R^{11})_2$, CSR^{11}, hidroxil C_1-C_6 alquil-R^{11}, amino C_1-C_4 alquil-R^7, amino, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, $N=N(R^7)$, $N(R^7)$-$N=C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, $ON=C(R^{11})$, C_1-C_{10} alquil-NHR^7, C_1-C_{10} alquil-NR^8R^9, (C_1-C_{10})alquil-$N(R^7)$-$N(R^8)(R^9)$, (C_1-C_{10})alquil$C(R^{11})$=N-$N(R^8)(R^9)$,(C_1-C_{10})alquil-$N=N(R^7)$, (C_1-C_{10})alquil-$N(R^7)$-$N=C(R^8)$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{10}, C_1-C_{10} alquil-OR^{10}, COR^{11}, CO_2R^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_{10} alquil-COR^{11}, C_1-C_{10} alquil-SR^{10}, C_1-C_{10} alquil-SOR^{11}, C_1-C_{10} alquil-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{13} y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{23}, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alquil-OR^{21}, CO_2R^{21}, COR^{21}, $C(S)OR^{21}$, $C(O)SR^{21}$, $C(O)R^{23}$, $C(S)R^{23}$, $CONHR^{22}$, $C(S)NHR^{22}$, $CON(R^{22})_2$, $C(S)N(R^{22})_2$, SR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_6 alquil-CO_2R^{21}, C_1-C_6 alquil-$C(S)OR^{21}$, C_1-C_6 alquil-$C(O)SR^{21}$, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$C(S)R^{23}$, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-$C(S)NHR^{22}$, C_1-C_6 alquil-$CON(R^{22})_2$, C_1-C_6 alquil-$C(S)N(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{15} y R^{16} se seleccionan independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$, C_1-C_4 alquil-OR^{21}, CSR^{11}, CO_2R^{22}, COR^{23}, $CONHR^{22}$, $CON(R^{22})_2$, SOR^{23}, SO_2R^{23}, C_1-C_6 alquil-CO_2R^{22}, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-$CON(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{19}, C_1-C_6 alquil-R^{19}, C_2-C_6 alquinilo, amino, NHR^{19}, $NR^{19}R^{20}$, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alquil-OR^{21}, SR^{21}, C_1-C_6 alquil-CO_2R^{21}, C_1-C_6 alquil-$C(S)OR^{21}$, C_1-C_6 alquil-$C(O)SR^{21}$, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$C(S)R^{23}$, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-

C(S)NHR^{22}, C_1-C_6 alquil-CON(R^{22})$_2$, C_1-C_6 alquil-C(S)N(R^{22})$_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{23}, C_2-C_{10} alquenil-R^{23}, C_2-C_{10} alquinil-R^{23}, C_1-C_{10} alquil-(R^{23})$_2$, C_2-C_{10} alquenil (R^{23})$_2$, CSR^{23}, amino, NHR^{19}, NR^{20}R^{20}, N(R^{19})-N(R^{20})(R^{20}), C(R^{23})=N-N(R^{20})(R^{20}), N=N(R^{19}), N(R^{19})-N=C(R^{20}), C(R^{23})=N-O(R^{21}), ON=C(R^{23}), C_1-C_{10} alquil-NHR^{19}, C_1-C_{10} alquil-NR^{20}R^{20}, (C_1-C_{10})alquil-N(R^{19})-N(R^{20})(R^{20}), (C_1-C_{10})alquilC(R^{23})=N-N(R^{20})(R^{20}), (C_1-C_{10})alquil-N=N(R^{19}), (C_1-C_{10})alquil-N(R^{19})-N=C(R^{20}), SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{21}, C_1-C_{10} alquil-OR^{21}, COR^{23}, CO_2R^{23}, SR^{21}, SSR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_{10} alquil-COR^{23}, C_1-C_{10} alquil-SR^{21}, C_1-C_{10} alquil-SOR^{23}, C_1-C_{10} alquil-SO_2R^{23}, halo, Si(R^{23})$_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{29}, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-NR^{25}R^{26}, O-R^{27}, C_1-C_4 alquil-OR^{27}, CO_2R^{27}, C(S)OR^{27}, C(O)SR^{27}, C(O)R^{29}, C(S)R^{29}, CONHR^{28}, C(S)NHR^{28}, CON(R^{28})$_2$, C(S)N(R^{28})$_2$, SR^{27} SOR^{29}, SO_2R^{29}, C_1-C_6 alquil-CO_2R^{27}, C_1-C_6 alquil-C(S)OR^{27}, C_1-C_6 alquil-C(O)SR^{27}, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-

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$C(S)R^{29}$, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$C(S)NHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-$C(S)N(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan independientemente de -H, C_1-C_{10} alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, C_1-C_4 alquil-OR^{27}, CSR^{11}, CO_2R^{28}, COR^{29}, $CONHR^{28}$, $CON(R^{28})_2$, SOR^{29}, SO_2R^{29}, C_1-C_6 alquil-CO_2R^{28}, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{23} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{25}, C_1-C_6 alquil-R^{25}, C_2-C_6 alquinilo, amino, NHR^{25}, $NR^{25}R^{26}$, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alquil-OR^{27}, SR^{27}, C_1-C_6 alquil-CO_2R^{27}, C_1-C_6 alquil-$C(S)OR^{27}$, C_1-C_6 alquil-$C(O)SR^{27}$, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$C(S)R^{29}$, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$C(S)NHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-$C(S)N(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo,

heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{24} se selecciona de -H, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{29}, C_2-C_{10} alquenil-R^{29}, C_2-C_{10} alquinil-R^{29}, C_1-C_{10} alquil-$(R^{29})_2$, C_2-C_{10} alquenil-$(R^{29})_2$, CSR^{29}, amino, NHR^{25}, $NR^{26}R^{26}$, $N(R^{25})$-$N(R^{26})(R^{26})$, $C(R^{29})$=N-$N(R^{26})(R^{26})$, N=$N(R^{25})$, $N(R^{25})$-N=$C(R^{26})$, $C(R^{29})$=N-$O(R^{27})$, ON=$C(R^{29})$, C_1-C_{10} alquil-NHR^{25}, C_1-C_{10} alquil-$NR^{26}R^{26}$, (C_1-C_{10})alquil-$N(R^{25})$-$N(R^{26})(R^{26})$,(C_1-C_{10})alquil$C(R^{29})$=N-$N(R^{26})(R^{26})$, (C_1-C_{10})alquil-N=$N(R^{25})$, (C_1-C_{10})alquil-$N(R^{25})$-N=$C(R^{26})$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{27}, C_1-C_{10} alquil-OR^{27}, CO_2R^{29}, COR^{29}, SR^{27}, SSR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_{10} alquil-COR^{29}, C_1-C_{10} alquil-SR^{27}, C_1-C_{10} alquil-SOR^{29}, C_1-C_{10} alquil-SO_2R^{29}, halo, $Si(R^{29})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{25} y R^{26} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{35}, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alquil-OR^{33}, CO_2R^{33}, $C(S)OR^{33}$, $C(O)SR^{33}$, $C(O)R^{35}$, $C(S)R^{35}$, $CONHR^{34}$, $C(S)NHR^{34}$, $CON(R^{34})_2$, $C(S)N(R^{34})_2$; SR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_6 alquil-CO_2R^{33}, C_1-C_6 alquil-$C(S)OR^{33}$, C_1-C_6 alquil-$C(O)SR^{33}$, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$C(S)R^{35}$, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$C(S)NHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-$C(S)N(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo,

alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{27} y R^{28} se seleccionan independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, C_1-C_4 alquil-OR^{33}, CSR^{11}, CO_2R^{34}, COR^{35}, $CONHR^{34}$, $CON(R^{34})_2$, SOR^{35}, SO_2R^{35}, C_1-C_6 alquil-CO_2R^{34}, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{29} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{31}, C_1-C_6 alquil-R^{31}, C_2-C_6 alquinilo, amino, NHR^{31}, $NR^{31}R^{32}$, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alquil-OR^{33}, SR^{33}, C_1-C_6 alquil-CO_2R^{33}, C_1-C_6 alquil-$C(S)OR^{33}$, C_1-C_6 alquil-$CO(O)SR^{33}$, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$C(S)R^{35}$, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$C(S)NHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-$C(S)N(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{30} se selecciona de -H, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{35}, C_2-C_{10} alquenil-R^{35}, C_2-C_{10} alquinil-R^{35}, C_1-C_{10} alquil-$(R^{35})_2$, C_2-C_{10} alquenil-$(R^{35})_2$, CSR^{35}, amino, NHR^{31}, $NR^{32}R^{32}$,

N(R^{31})-N(R^{32})(R^{32}), C(R^{35})=N-N(R^{32})(R^{32}), N=N(R^{31}), N(R^{31})-N=C(R^{32}), C(R^{35})=N-O(R^{33}), ON=C(R^{35}), C_1-C_{10} alquil-NHR^{31}, C_1-C_{10} alquil-N$R^{32}R^{32}$, (C_1-C_{10})alquil-N(R^{31})-N(R^{32})(R^{32}), (C_1-C_{10})alquilC(R^{35})=N-N(R^{32})(R^{32}), (C_1-C_{10})alquil-N=N(R^{31}), (C_1-C_{10})alquil-N(R^{31})-N=C(R^{32}), SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{33}, C_1-C_{10} alquil-OR^{33}, COR^{35}, SR^{33}, SSR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_{10} alquil-COR^{35}, C_1-C_{10} alquil-SR^{33}, C_1-C_{10} alquil-SOR^{35}, C_1-C_{10} alquil-SO_2R^{35}, halo, Si(R^{35})$_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{31}, R^{32}, R^{33} y R^{34} se seleccionan cada uno independientemente de -H, alquilo, alquenilo, alquinilo, aminoalquilo, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{35} se selecciona de -H, alquilo, alquenilo, alquinilo, aminoalquilo, OH, alcoxi, amino, alquilamino, dialquilamino, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H, alquilo, alquenilo, alquinilo, aminoalquilo, OH, alcoxi, amino, nitro, ciano, halo, alquilamino, dialquilamino, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heterociclilalquilo, y heteroarilalquilo;

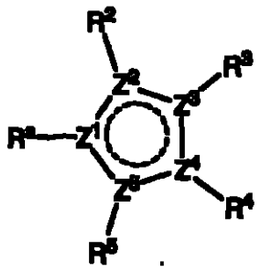
R^2, R^3, R^4, R^5, R^{37} y R^{38} cada uno independientemente están ausentes, o se seleccionan de un grupo R^1;

n es 0; y

R^3 y R^4 se juntan de manera opcional para formar un anillo de 5, 6, 7, u 8 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

[00014] La presente invención se dirige igualmente a un compuesto novedoso con la estructura de fórmula II:

Fórmula II.

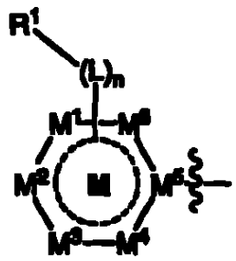


en donde:

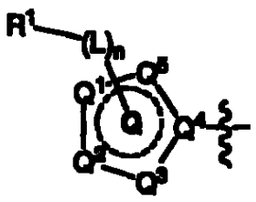
Z^2 y Z^3 son nitrógeno, Z^1, Z^4 y Z^5 son carbono, y se juntan con Z^2 y Z^3 para formar un anillo pirazol, o de manera opcional, Z^4 y Z^5 son nitrógeno, Z^1, Z^2 y Z^3 son carbono y se juntan con Z^4 y Z^5 para formar un anillo pirazol;

R^a se selecciona de:

1)



2)



, y

3)



donde las líneas discontinuas indican enlaces simples o dobles opcionales;

cuando R^a es anillo M y anillo M es aromático, M^1 es carbono y es sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono y nitrógeno y es no sustituido o sustituido con $(L)_nR^1$;

cuando anillo M es parcialmente saturado, M^1 es carbono y es mono- o di-sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y cuando M^2, M^3, M^4, o M^6 es oxígeno o azufre, es no sustituido, y cuando M^2, M^3, M^4 o M^6 es carbono o nitrógeno, es opcionalmente no sustituido; o mono- o di-sustituido con $(L)_nR^1$;

cuando R^a es anillo Q y anillo Q es aromático, Q^1 se selecciona de carbono y nitrógeno, y cuando Q^1 es carbono, se sustituye con $(L)_nR^1$, y cuando Q^1 es nitrógeno, es no sustituido, Q^4 se selecciona de nitrógeno y carbono, y cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de

nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

opcionalmente, cuando anillo Q es aromático, Q^1 es carbono y es sustituido con $(L)_nR^1$, Q^4 es carbono, y uno de Q^2, Q^3 y Q^5 es opcionalmente oxígeno o azufre, y el resto de Q^2, Q^3 y Q^5 se seleccionan independientemente de nitrógeno y carbono, y si carbono, se sustituyen con $(L)_nR^1$;

cuando anillo Q es parcialmente saturado, Q^1 se selecciona de carbono y nitrógeno, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$, Q^4 se selecciona de carbono y nitrógeno, pero sólo uno de Q^1 y Q^4 puede ser nitrógeno, cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y si oxígeno o azufre, es no sustituido, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$;

cuando R^a es estructura 3, es completamente conjugado, X^2 se selecciona de oxígeno o nitrógeno sustituido con $(L)_nR^1$, X^1 es carbono y es sustituido con $(L)_nR^1$, y cada uno de X^5 y X^6 se selecciona independientemente de nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, hidroxilo, C_1-C_6 alcoxi, C_2-C_6 alquenil-R^{11}, C_1-C_6 alcoxi-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alquilo, hidroxi C_1-C_4 alquilo, amino, amino C_1-C_4 alquil-R^7, halo C_1-C_4 alquilo, C_1-C_6 alquil-NHR^7, carbonitrilo, SR^{10}, halo, NHR^7 NR^8R^9, NHR^7-C_1-C_6 alquilo, NR^8R^9-C_1-C_6 alquilo, nitro, ciano, O-R^{10}, C_1-C_4 alquil-OR^{10}, C_1-C_6 alquil-COR^{11}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, o C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{12};

R^7 y R^8 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, arilo, y

arilalquilo, en donde arilo y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^9 y R^{10} se seleccionan cada uno independientemente de -H, hidroxilo, C_1-C_6 alquilo, C_1-C_6 alquil-R^{17}, C_1-C_6 alquil-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alquil-CO_2R^{16}, C_1-C_6 alquil-CONH-R^{16}, C_1-C_6 alquil-$CON(R^{16})_2$, hidroxi C_1-C_4 alquilo, halo C_1-C_4 alcoxi, halo C_1-C_4 alquilo, $Si(R^{13})_2R^{17}$ arilo, heteroarilo, heterociclilo, arilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxilo, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo, y heterociclilalquilo, en donde heterociclilo, heteroarilalquilo, y heterociclilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, hidroxilo, oxo, C_1-C_6 alquilo, hidroxil C_1-C_6 alquil-R^{11}, C_1-C_{10} alcoxi, amino, amino C_1-C_4 alquil-R^7, NHR^7, $N(R^7)_2$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NHR^8R^9, C_1-C_6 alquil-$N(R^8)_2$, C_1-C_6 alquil-R^{11}, C_1-C_6 alquil-$CO_2R^7R^{11}$, C_1-C_6 alcoxi-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_6 alquil-SR^{10}, halo, halo C_1-C_4 alquilo, halo C_1-C_4 alcoxi, hidroxi C_1-C_4 alquilo, hidroxi C_1-C_4 alcoxi, arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, y heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{13}y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, COR^{23}, y arilo;

R^{15} y R^{16} se seleccionan cada uno independientemente de -H, arilo, arilalquilo, en donde arilo, arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alquil-R^{19}, NHR^{19}, arilo,

heteroarilalquilo, y heterociclilalquilo, en donde arilo se sustituye opcionalmente con uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, hidroxilo, C_1-C_{10} alquilo, C_1-C_{10} alcoxi, amino, amino C_1-C_6 alquilo, $N(R^{19})_2$, C_1-C_6 alquil-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, y heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, heteroarilo, heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan cada uno independientemente de -H y C_1-C_6 alquilo;

R^{23} se selecciona de -H y C_1-C_6 alquilo;

R^{24} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, CO_2R^{29}, halo, y halo C_1-C_4 alquilo;

R^{29} se selecciona de -H, y C_1-C_6 alquilo;

R^{30} se selecciona de -H, arilo, heteroarilo, heterociclilo, alquilarilo, arilalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H y halo;

R^2, R^3, R^4, R^{37} y R^{38} se seleccionan cada uno independientemente de un grupo R^1;

n es 0; y

R^3 y R^4 se juntan de manera opcional para formar un anillo de 5, 6, 7, u 8 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

[00015] La presente invención se dirige igualmente a un compuesto novedoso inhibidor de MK-2 que se enumera en la Tabla I o Tabla II, más adelante.

[00016] La presente invención se dirige igualmente a un método novedoso de inhibir MK-2, método que comprende poner en contacto MK-2 con por lo menos un compuesto que se describe en Tabla I o Tabla II, más adelante.

[00017] La presente invención se dirige igualmente a método novedoso de prevenir o tratar una enfermedad o trastorno mediado por TNFα en un individuo, método que comprende administrar al individuo una cantidad efectiva de un compuesto inhibidor de MK-2 con la estructura descrita en fórmula I.

[00018] La presente invención se dirige igualmente a método novedoso de prevenir o tratar una enfermedad o trastorno mediado por TNFα en un individuo, método que comprende administrar al individuo por lo menos un compuesto inhibidor de MK-2 que se describe en Tabla I o Tabla II, más adelante.

[00019] La presente invención se dirige igualmente a una novedosa composición terapéutica que comprende un compuesto con la estructura descrita en fórmula I.

[00020] La presente invención se dirige igualmente a una novedosa composición terapéutica que comprende por lo menos un compuesto inhibidor de MK-2 que se describe en Tabla I o Tabla II.

[00021] La presente invención se dirige igualmente a una novedosa composición farmacéutica que comprende un vehículo farmacéuticamente aceptable y por lo menos un compuesto inhibidor de MK-2 con la estructura descrita en fórmula I.

[00022] La presente invención se dirige igualmente a una novedosa (sic) que comprende una formulación farmacéutica que incluye una cantidad terapéuticamente efectiva de por lo menos un compuesto inhibidor de MK-2 con una estructura descrita en fórmula I.

[00023] Por consiguiente, entre las varias ventajas que, tal como se descubrió, se logran por la presente invención, pueden anotarse la provisión de un método que podría servir para modular la actividad de MK-2 – en particular, inhibir la actividad MK-2 – y la provisión de un método para la prevención y tratamiento de enfermedades y trastornos mediados por TNFα.

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BREVE DESCRIPCIÓN DE LOS DIBUJOS

[00024] Figura 1 es un gráfico que muestra el espesor de la garra como una función del tiempo del día 0 al día 7 para ratones MK2 (+/+) y MK2 (-/-), que habían recibido inyección de suero; y

[00025] Figura 2 es un cuadro de barras que muestra el espesor de la garra siete días después de la inyección para ratones normales, ratones MK2 (+/+) que recibían suero, ratones MK2 (-/-) que recibían suero, y ratones MK2 (+/+) que recibían suero y anticuerpo anti-TNF;

DESCRIPCIÓN DETALLADA DE LAS INCORPORACIONES PREFERIDAS

[00026] De acuerdo con la presente invención, se ha descubierto que ciertos compuestos pueden inhibir la actividad de MAPKAP cinasa-2. Muchos de estos compuestos exhiben su efecto inhibidor con bajas concentraciones – teniendo valores IC_{50} de inhibición de MK-2 *in vitro* de por debajo de 1.0 μM, y con algunos teniendo valores IC_{50} de por debajo de alrededor de 0.1 μM, e incluso tan bajos como alrededor de 0.02 μM. Por consiguiente, estos compuestos pueden ser medicamentos potentes y efectivos para uso en la inhibición de MK-2, y de valor especial en individuos en los que tal inhibición sería útil. En particular, estos compuestos serían útiles en métodos para prevenir o tratar enfermedades y trastornos que son mediados por TNFα. Por ejemplo, pueden usarse para la prevención o tratamiento de artritis.

[00027] Compuestos que poseen un alto grado de actividad inhibidora de MK-2 ofrecen ventajas en usos terapéuticos, ya que pueden obtenerse beneficios terapéuticos por la administración de menores cantidades de los presentes compuestos que con compuestos menos activos. Tales compuestos altamente activos se traducen además en menores efectos colaterales y, en algunas incorporaciones, demuestran una selectividad para

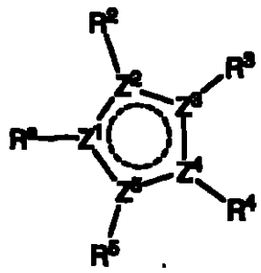
la inhibición de MK-2 sobre la inhibición de otras cinasas relacionadas.

[00028] Los presentes compuestos inhibidores de MK-2 inhiben la actividad de la enzima MK-2. Cuando se dice que un compuesto tal inhibe MK-2, se da a entender que la actividad enzimática MK-2 es menor en la presencia del compuesto que lo que es bajo las mismas condiciones en la ausencia de tal compuesto. Un método de expresar la potencia de un compuesto como un inhibidor de MK-2 es cuantificar el valor "IC_{50}" del compuesto. El valor IC_{50} de un inhibidor de MK-2 es la concentración del compuesto que se requiere para disminuir la actividad enzimática MK-2 en la mitad. Por consiguiente, se considera que un compuesto con un valor IC_{50} más bajo es un inhibidor más potente que un compuesto que tiene un valor IC_{50} más alto. Tal como se emplea aquí, los compuestos que inhiben MK-2 pueden denominarse inhibidores de MK-2, o compuestos inhibidores de MK-2 o agentes inhibidores de MK-2.

[00029] En la práctica, la selectividad de un inhibidor de MK-2 varía dependiendo de la condición bajo la cual se lleva a cabo la prueba y de los inhibidores que se están probando. No obstante, para los efectos de esta especificación, la selectividad de un inhibidor de MK-2 puede cuantificarse como una proporción del valor IC_{50} *in vitro* o *in vivo* para inhibición de MK-3, dividida por el valor IC_{50} para inhibición de MK-2 ($IC_{50\ MK-3}/IC_{50\ MK-2}$). Tal como se emplea aquí, el término "IC_{50}" se refiere a la concentración de un compuesto que se requiere para producir una inhibición del 50% de la actividad MK-2 o MK-3. Un inhibidor selectivo de MK-2 es cualquier inhibidor para el cual la proporción de $IC_{50\ MK-3}$ a $IC_{50\ MK-2}$ es mayor que 1. En incorporaciones preferidas, esta proporción es mayor que 2, más preferiblemente mayor que 5, aún más preferiblemente mayor que 10, todavía más preferiblemente mayor que 50, y más preferiblemente aún, es mayor que 100. Tal selectividad preferida puede indicar una capacidad de reducir la incidencia de efectos colaterales de probable ocurrencia con la administración de un inhibidor de MK-2 a un individuo.

[00030] Compuestos que son útiles en el presente método incluyen aquellos que tienen la estructura mostrada en fórmula I:

Fórmula I:

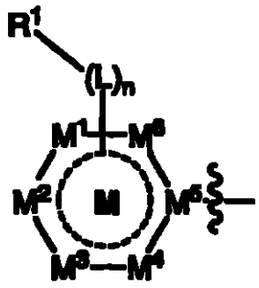


en donde:

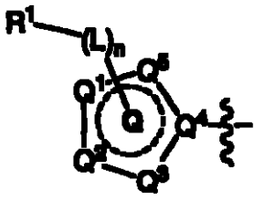
Z^2 y Z^3 son nitrógeno, Z^1, Z^4 y Z^5 son carbono, y se juntan con Z^2 y Z^3 para formar un anillo pirazol, o de manera opcional, Z^4 y Z^5 son nitrógeno, Z^1, Z^2 y Z^3 son carbono y se juntan con Z^4 y Z^5 para formar un anillo pirazol;

R^a se selecciona de:

1)



2)



, y

3)



donde las líneas discontinuas indican enlaces simples o dobles opcionales;

cuando R^a es anillo M y anillo M es aromático, M^1 es carbono y es sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono y nitrógeno y es no sustituido o sustituido con $(L)_nR^1$;

cuando anillo M es parcialmente saturado, M^1 es carbono y es mono- o di-sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y, cuando M^2, M^3, M^4, o M^6 es oxígeno o azufre, es no sustituido, y cuando M^2, M^3, M^4 o M^6 es carbono o nitrógeno, es opcionalmente no sustituido; o mono- o di-sustituido con $(L)_nR^1$;

cuando R^a es anillo Q y anillo Q es aromático, Q^1 se selecciona de carbono y nitrógeno, y cuando Q^1 es carbono, se sustituye con $(L)_nR^1$, y cuando Q^1 es nitrógeno, es no sustituido, Q^4 se selecciona de nitrógeno y carbono, y cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

opcionalmente, cuando anillo Q es aromático, Q^1 es carbono y es sustituido con $(L)_nR^1$, Q^4 es carbono, y uno de Q^2, Q^3 y Q^5 es opcionalmente oxígeno o azufre, y el resto de Q^2, Q^3 y Q^5 se seleccionan independientemente de nitrógeno y carbono, y si carbono, se sustituyen con $(L)_nR^1$;

cuando anillo Q es parcialmente saturado, Q^1 se selecciona de carbono y nitrógeno, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$, Q^4 se selecciona de carbono y nitrógeno, pero sólo uno de Q^1 y Q^4 puede ser nitrógeno, cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y si oxígeno o azufre, es no sustituido, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$;

cuando R^a es estructura 3, es completamente conjugado, X^2 se selecciona de oxígeno o nitrógeno sustituido con $(L)_nR^1$, X^1 es carbono y es sustituido con $(L)_nR^1$, y cada uno de X^5 y X^6 se selecciona independientemente de nitrógeno y carbono, y si carbono, se sustituye con

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$(L)_nR^1$;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-R^{11}, C_2-C_6 alquenil-R^{11}, C_2-C_6 alquinil-R^{11}, C_1-C_6 alquil-$(R^{11})_2$, C_2-C_6 alquenil-$(R^{11})_2$, CSR^{11}, amino, $CONHR^{11}$, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NR^8R^9, $(C_1$-$C_4)$alquil-$N(R^7)$-$N(R^8)(R^9)$, $(C_1$-$C_4)$alquil$C(R^{11})$=N-$N(R^8)(R^9)$, $(C_1$-$C_4)$alquil-N=$N(R^7)$, $(C_1$-$C_4)$alquil-$N(R^7)$-N=$C(R^8)$, nitro, ciano, CO_2R^{11}, O-R^{10}, C_1-C_4 alquil-OR^{10}, COR^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_6alquil-COR^{11}, C_1-C_6 alquil-SR^{10}, C_1-C_6 alquil-SOR^{11}, C_1-C_6 alquil-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{12};

R^7, R^8 y R^9 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alquil-OR^{15}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, $C(O)R^{17}$, $C(S)R^{17}$, $CONHR^{16}$, $C(S)NHR^{16}$, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SR^{15}, SOR^{17}, SO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$ C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{10} se selecciona de -H, C_1-C_{10} alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, C_1-C_4 alquil-OR^{15}, CSR^{11}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, COR^{17}, $C(S)R^{17}$, $CONHR^{16}$, C_1-C_4 alquil-R^{11}, C_1-C_4 alquil-NH_2R^{13}, $C(S)NHR^{16}$, O-R^{15}, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SOR^{17}, SO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, $Si(R^{13})_2R^{17}$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_2-C_6 alquenilo, C_2-C_6 alquinilo, amino, NHR^{13}, $NR^{13}R^{14}$, $N{=}NR^{13}$, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alquil-OR^{15}, SR^{15}, COR^{13}, CO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, OH, oxo, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{11}, C_2-C_{10} alquenil-R^{11}, C_2-C_{10} alquinil-R^{11}, C_1-C_{10} alquil-$(R^{11})_2$, C_2-C_{10} alquenil-$(R^{11})_2$, CSR^{11}, hidroxil C_1-C_6 alquil-

R^{11}. amino C_1-C_4 alquil-R^7 amino, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_{10} alquil-NHR^7, C_1-C_{10} alquil-NR^8R^9, (C_1-C_{10})alquil-$N(R^7)$-$N(R^8)(R^9)$, (C_1-C_{10})alquil$C(R^{11})$=N-$N(R^8)(R^9)$, (C_1-C_{10})alquil-N=$N(R^7)$,(C_1-C_{10})alquil-$N(R^7)$-N=$C(R^8)$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{10}, C_1-C_{10} alquil-OR^{10}, COR^{11}, CO_2R^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_{10} alquil-COR^{11}, C_1-C_{10} alquil-SR^{10}, C_1-C_{10} alquil-SOR^{11}, C_1-C_{10} alquil-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{13} y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{23}, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alquil-OR^{21}, CO_2R^{21}, COR^{21}, $C(S)OR^{21}$, $C(O)SR^{21}$, $C(O)R^{23}$, $C(S)R^{23}$, $CONHR^{22}$, $C(S)NHR^{22}$, $CON(R^{22})_2$, $C(S)N(R^{22})_2$, SR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_6 alquil-CO_2R^{21}, C_1-C_6 alquil-$C(S)OR^{21}$, C_1-C_6 alquil-$C(O)SR^{21}$, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$C(S)R^{23}$, C_1-C_6 alquil-$CONHR^{22}$ C_1-C_6 alquil-$C(S)NHR^{22}$, C_1-C_6 alquil-$CON(R^{22})_2$, C_1-C_6 alquil-$C(S)N(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{15} y R^{16} se seleccionan independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$,

C_1-C_4 alquil-OR^{21}, CSR^{11}, CO_2R^{22}, COR^{23}, $CONHR^{22}$, $CON(R^{22})_2$, SOR^{23}, SO_2R^{23}, C_1-C_6 alquil-CO_2R^{22}, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-$CON(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{19}, C_1-C_6 alquil-R^{19}, C_2-C_6 alquinilo, amino, NHR^{19}, $NR^{19}R^{20}$, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alquil-OR^{21}, SR^{21}, C_1-C_6 alquil-CO_2R^{21}, C_1-C_6 alquil-$C(S)OR^{21}$, C_1-C_6 alquil-$C(O)SR^{21}$, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$C(S)R^{23}$, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-$C(S)NHR^{22}$, C_1-C_6 alquil-$CONCR^{22})_2$, C_1-C_6 alquil-$C(S)N(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{23}, C_2-C_{10} alquenil-R^{23}, C_2-C_{10} alquinil-R^{23}, C_1-C_{10} alquil-$(R^{23})_2$, C_2-C_{10} alquenil-$(R^{23})_2$, CSR^{23}, amino, NHR^{19}, $NR^{20}R^{20}$, $N(R^{19})$-$N(R^{20})(R^{20})$, $C(R^{23})$=N-$N(R^{20})(R^{20})$, N=$N(R^{19})$, $N(R^{19})$-N=$C(R^{20})$, $C(R^{23})$=N-$O(R^{21})$, ON=$C(R^{23})$, C_1-C_{10} alquil-NHR^{19}, C_1-C_{10} alquil-$NR^{20}R^{20}$, (C_1-C_{10})alquil-$N(R^{19})$-$N(R^{20})(R^{20})$,(C_1-C_{10})alquil$C(R^{23})$=N-$N(R^{20})$ (R^{20}), (C_1-C_{10})alquil-N=$N(R^{19})$, (C_1-C_{10})alquil-$N(R^{19})$-N=$C(R^{20})$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{21}, C_1-C_{10} alquil-OR^{21},

COR^{23}, CO_2R^{23}, SR^{21}, SSR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_{10} alquil-COR^{23}, C_1-C_{10} alquil-SR^{21}, C_1-C_{10} alquil-SOR^{23}, C_1-C_{10} alquil-SO_2R^{23}, halo, $Si(R^{23})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{29}, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alquil-OR^{27}, CO_2R^{27}, $C(S)OR^{27}$, $C(O)SR^{27}$, $C(O)R^{29}$, $C(S)R^{29}$, $CONHR^{28}$, $C(S)NHR^{28}$, $CON(R^{28})_2$, $C(S)N(R^{28})_2$, SR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_6 alquil-CO_2R^{27}, C_1-C_6 alquil-$C(S)OR^{27}$, C_1-C_6 alquil-$C(O)SR^{27}$, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$C(S)R^{29}$, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$C(S)NHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-$C(S)N(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan independientemente de -H, C_1-C_{10} alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, C_1-C_4 alquil-OR^{27}, CSR^{11}, CO_2R^{28}, COR^{29}, $CONHR^{28}$, $CON(R^{28})_2$, SOR^{29}, SO_2R^{29}, C_1-C_6 alquil-CO_2R^{28}, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico

cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{23} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{25}, C_1-C_6 alquil-R^{25}, C_2-C_6 alquinilo, amino, NHR^{25}, $NR^{25}R^{26}$, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alquil-OR^{27}, SR^{27}, C_1-C_6 alquil-CO_2R^{27}, C_1-C_6 alquil-$C(S)OR^{27}$, C_1-C_6 alquil-$C(O)SR^{27}$, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$C(S)R^{29}$, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$C(S)NHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-$C(S)N(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{24} se selecciona de -H, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{29}, C_2-C_{10} alquenil-R^{29}, C_2-C_{10} alquinil-R^{29}, C_1-C_{10} alquil-$(R^{29})_2$, C_2-C_{10} alquenil$(R^{29})_2$, CSR^{29}, amino, NHR^{25}, $NR^{26}R^{26}$, $N(R^{25})$-$N(R^{26})(R^{26})$, $C(R^{29})$=N-$N(R^{26})(R^{26})$, $N=N(R^{25})$, $N(R^{25})$-$N=C(R^{26})$, $C(R^{29})$=N-$O(R^{27})$, $ON=C(R^{29})$, C_1-C_{10} alquil-NHR^{25}, C_1-C_{10} alquil-$NR^{26}R^{26}$, (C_1-C_{10})alquil-$N(R^{25})$-$N(R^{26})(R^{26})$,(C_1-C_{10})alquil$C(R^{29})$=N-$N(R^{26})(R^{26})$,(C_1-C_{10})alquil-$N=N(R^{25})$, (C_1-C_{10})alquil-$N(R^{25})$-$N=C(R^{26})$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{27}, C_1-C_{10} alquil-OR^{27}, CO_2R^{29}, COR^{29}, SR^{27}, SSR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_{10} alquil-COR^{29}, C_1-C_{10} alquil-SR^{27}, C_1-C_{10} alquil-SOR^{29}, C_1-C_{10} alquil-SO_2R^{29}, halo, $Si(R^{29})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo,

arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{25} y R^{26} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{35}, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alquil-OR^{33}, CO_2R^{33}, $C(S)OR^{33}$, $C(O)SR^{33}$, $C(O)R^{35}$, $C(S)R^{35}$, $CONHR^{34}$, $C(S)NHR^{34}$, $CON(R^{34})_2$, $C(S)N(R^{34})_2$, SR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_6 alquil-CO_2R^{33}, C_1-C_6 alquil-$C(S)OR^{33}$, C_1-C_6 alquil-$C(O)SR^{33}$, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$C(S)R^{35}$, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$C(S)NHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-$C(S)N(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{27} y R^{28} se seleccionan independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, C_1-C_4 alquil-OR^{33}, CSR^{11}, CO_2R^{34}, COR^{35}, $CONHR^{34}$, $CON(R^{34})_2$, SOR^{35}, SO_2R^{35}, C_1-C_6 alquil-CO_2R^{34}, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{29} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{31}, C_1-C_6 alquil-R^{31}, C_2-C_6 alquinilo, amino, NHR^{31}, $NR^{31}R^{32}$, C_1-C_6

alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alquil-OR^{33}, SR^{33}, C_1-C_6 alquil-CO_2R^{33}, C_1-C_6 alquil-$C(S)OR^{33}$, C_1-C_6 alquil-$C(O)SR^{33}$, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$C(S)R^{35}$, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$C(S)NHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-$C(S)N(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquil. arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{30} se selecciona de -H, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{35}, C_2-C_{10} alquenil-R^{35}, C_2-C_{10} alquinil-R^{35}, C_1-C_{10} alquil-$(R^{35})_2$, C_2-C_{10} alquenil$(R^{35})_2$, CSR^{35}, amino, NHR^{31}, $NR^{32}R^{32}$, $N(R^{31})$-$N(R^{32})(R^{32})$, $C(R^{35})$=N-$N(R^{32})(R^{32})$, N=$N(R^{31})$, $N(R^{31})$-N=$C(R^{32})$, $C(R^{35})$=N-$O(R^{33})$, ON=(R^{35}), C_1-C_{10}alquil-NHR^{31}, C_1-C_{10} alquil-$NR^{32}R^{32}$, (C_1-C_{10})alquil-$N(R^{31})$-$N(R^{32})(R^{32})$, (C_1-C_{10})alquil$C(R^{35})$=N-$N(R^{32})(R^{32})$, (C_1-C_{10})alquil-N=$N(R^{31})$, (C_1-C_{10})alquil-$N(R^{31})$-N=$C(R^{32})$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{33}, C_1-C_{10} alquil-OR^{33}, COR^{35}, SR^{33}, SSR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_{10} alquil-COR^{35}, C_1-C_{10} alquil-SR^{33}, C_1-C_{10} alquil-SOR^{35}, C_1-C_{10} alquil-SO_2R^{35}, halo, $Si(R^{35})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{31}, R^{32}, R^{33} y R^{34} se seleccionan cada uno independientemente de -H, alquilo, alquenilo, alquinilo, aminoalquilo, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo,

alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{35} se selecciona de -H, alquilo, alquenilo, alquinilo, aminoalquilo, OH, alcoxi, amino, alquilamino, dialquilamino, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H, alquilo, alquenilo, alquinilo, aminoalquilo, OH, alcoxi, amino, nitro, ciano, halo, alquilamino, dialquilamino, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heterociclilalquilo, y heteroarilalquilo;

R^2, R^3, R^4, R^5, R^{37} y R^{38} cada uno independientemente están ausentes, o se seleccionan de un grupo R^1;

n es 0; y

R^3 y R^4 se juntan de manera opcional para formar un anillo de 5, 6,7, u 8 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

[00031] El anillo "M" y el anillo "Q" de la estructura de fórmula I pueden tener cualquier número de grupos sustituyentes R^1-L_n-, fluctuando de cero a uno o más por átomo del anillo, y tales grupos sustituyentes pueden localizarse en cualquier átomo del anillo con una valencia apropiada para la adición de un grupo (s) sustituyente (s). Cada tal grupo sustituyente puede

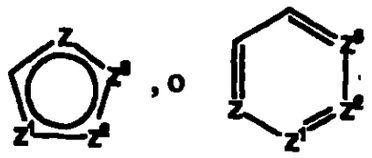
tener cualquier número de grupos R^1 por grupo L, fluctuando de cero a 5. Una estructura preferida es la presencia de 0 ó 1 grupo sustituyente R^1-L_n- en el anillo. Asimismo se prefiere que el grupo sustituyente R^1-L_n- se enlace al anillo en la localización M^1 o la Q^1, respectivamente.

[00032] El significado de cualquier sustituyente en cualquiera ocurrencia en Fórmula I, o cualquier otra fórmula química general indicada aquí, es independiente de sus significado, o del significado de cualquier otro sustituyente, en cualquier otra ocurrencia, a menos que se especifique lo contrario.

[00033] El término "alquilo" se usa, ya sea solo o dentro de otros términos tales como "haloalquilo" y "alquilsulfonilo"; éste abarca radicales lineales o ramificados que tienen uno hasta alrededor de veinte átomos de carbono o, preferiblemente, uno a alrededor de doce átomos de carbono. Radicales alquilo más preferidos son radicales "alquilo inferior" que tienen uno a alrededor de diez átomos de carbono. Muy preferidos son radicales alquilo inferior que tienen uno a alrededor de cinco átomos de carbono. El número de átomos de carbono puede expresarse también como "C_1-C_5", por ejemplo. Ejemplos de tales radicales incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isoamilo, hexilo, octilo y similares. El término "alquenilo" se refiere a un radical hidrocarburo acíclico, insaturado, lineal o ramificado, en la medida en que contenga por lo menos un enlace doble. A menos que se anote lo contrario, tales radicales contienen preferiblemente de 2 a alrededor de 6 átomos de carbono, preferiblemente de 2 a alrededor de 4 átomos de carbono, más preferiblemente de 2 a alrededor de 3 átomos de carbono. Los radicales alquenilo pueden sustituirse opcionalmente con grupos como los definidos más adelante. Ejemplos radicales alquenilo apropiados incluyen propenilo, 2-cloropropilenilo, buten-1-ilo, isobutenilo, penten-1-ilo, 2-metilbuten-1-ilo, 3-metilbuten-1-ilo, hexen-1-ilo, 3-hidroxihexen-1-ilo, hepten-1-ilo, octen-1-ilo, y similares. El término "alquinilo" se refiere a un radical hidrocarburo acíclico, insaturado, lineal o ramificado, en la medida en que contenga uno o más enlaces triples, conteniendo tales radicales

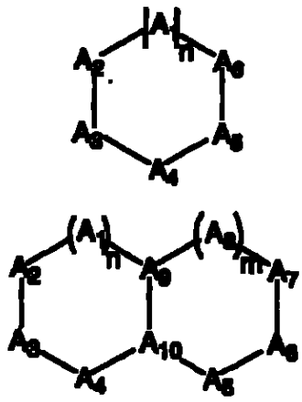
preferiblemente 2 a alrededor de 6 átomos de carbono, más preferiblemente de 2 a alrededor de 3 átomos de carbono. Los radicales alquinilo pueden sustituirse opcionalmente con grupos como los descritos más adelante. Ejemplos de radicales alquinilo apropiados incluyen radicales etinilo, propinilo, hidroxipropinilo, butin-1 -ilo, butin-2-ilo, pentin-1-ilo, pentin-2-ilo, 4-metoxipentin-2-ilo, 3-metilbutin-1-ilo, hexil-1-ilo, hexin-2-ilo, hexin-3-ilo, 3,3-dimetilbutin-1-ilo, y similares. El término "oxo" significa un solo oxígeno doblemente enlazado. Los términos "hidrido", "-H", o "hidrógeno", denotan un solo átomo de hidrógeno (H). Este radical hidrido puede enlazarse, por ejemplo, a un átomo de oxígeno para formar un radical hidroxilo, o dos radicales hidrido pueden enlazarse a un átomo de carbono para formar un radical (-CH_2-) metileno. El término "halo" significa halógenos tales como átomos de flúor, cloro, y bromo o yodo. El término "haloalquilo" abarca radicales en donde uno cualquiera o más de los átomos de carbono del alquilo se sustituye con halo como se define más arriba. Específicamente abarcados se encuentran radicales monohaloalquilo, dihaloalquilo, y polihaloalquilo. Un radical monohaloalquilo, por ejemplo, puede tener un átomo de bromo, cloro, o fluoro en el radical. Los radicales dihalo pueden tener dos o más de los mismos átomos halo o una combinación de diferentes radicales halo y radicales polihaloalquilo pueden tener más de dos de los mismos átomos halo o una combinación de diferentes radicales halo. Análogamente, el término "halo", cuando se yuxtapone a alquenilo, alquinilo, alcoxi, arilo, cicloalquilo, heteroalquilo, heteroarilo, y similares, incluye radicales que tienen sustitución mono-, di-, o tri-halo en uno o más de los átomos del radical. El término "hidroxialquilo" abarca radicales alquilo lineales o ramificados que tienen uno a alrededor de diez átomos de carbono, uno cualquiera de los cuales puede sustituirse con uno o más radicales hidroxilo. Los términos "alcoxi" y "alcoxialquilo" abarcan radicales que contienen oxi, lineales o ramificados, teniendo cada uno porciones alquilo de uno a alrededor de diez átomos de carbono, tales como un radical metoxi. El término "alcoxialquilo" abarca igualmente radicales alquilo que tienen dos o más

radicales alcoxi enlazados al radical alquilo, es decir, para formar radicales monoalcoxialquilo y dialcoxialquilo. Los radicales "alcoxi" o "alcoxialquilo" pueden sustituirse adicionalmente con uno o más átomos halo, tales como fluoro, cloro, o bromo, para proporcionar radicales "haloalcoxi" o "haloalcoxialquilo". Los ejemplos de radicales "alcoxi" incluyen metoxi, butoxi, y trifluorometoxi. Términos tales como "alcoxi(halo)alquilo" indican una molécula que tiene un terminal alcoxi que se une a un alquilo, el cual se enlaza a la molécula principal, mientras que el alquilo tiene también un grupo halo sustituyente en una localización no-terminal. En otras palabras, tanto el grupo alcoxi como el grupo halo son sustituyentes de la cadena alquilo. El término "arilo", solo o en combinación, significa un sistema aromático carbocíclico que contiene uno, dos, o tres anillos en donde tales anillos pueden unirse entre sí en una forma pendiente o pueden fusionarse. El término "arilo" abarca radicales aromáticos tales como fenilo, naftilo, tetrahidronaftilo, indano, y bifenilo. El término "heterociclilo" significa un carbociclo mono- o multi-anillo saturado o insaturado en donde uno o más átomos de carbono se reemplaza por N, S, P, ó O. Éste incluye, por ejemplo, estructuras tales como:



donde Z, Z^1, Z^2, o Z^3 es C, S, P, O, o N, con la condición que uno de Z, Z^1, Z^2, o Z^3 es distinto de carbono, pero no es O ó S cuando se une a otro átomo Z por un doble enlace o cuando se une a otro átomo O ó S. Más aún, se entiende que los sustituyentes óptimos se unen a Z, Z^1, Z^2, o Z^3 únicamente cuando cada uno es C. El término "heterociclo" incluye asimismo estructuras de anillo completamente saturado, tales como piperazinilo, dioxanilo, tetrahidrofuranilo, oxiranilo, aziridinilo, morfolinilo, pirrolidinilo, piperidinilo, tiazolidinilo, y otros. El término "heteroarilo" abarca radicales heterocíclicos insaturados. Ejemplos de

radicales heterocíclicos insaturados, también denominados radicales "heteroarilo" incluyen tienilo, pirrilo, furilo, piridilo, pirimidilo, pirazinilo, pirazolilo, oxazolilo, isoxazolilo, imidazolilo, tiazolilo, piranilo, y tetrazolilo. El término abarca igualmente radicales donde radicales heterocíclicos se fusionan con radicales arilo. Ejemplos de tales radicales bicíclico fusionados incluyen benzofurano, benzotiofeno, y similares. Los términos arilo o heteroarilo, según se apropiado, incluyen las siguientes estructuras:



donde:

cuando n=1, m=1 y A_1-A_8 son cada uno CR^x ó N, A_9 y A_{10} son carbono;

cuando n=0, ó 1, y m=0, ó 1, uno de A_2-A_4 y/o A_5-A_7 es opcionalmente S, O, o NR^x, y otros miembros del anillo son CR^x ó N, con la condición que oxígeno no puede estar adyacente a azufre en un anillo. A_9 y A_{10} son carbono;

cuando n es mayor que o igual a 0, y m es mayor que o igual a 0, 1 o más conjuntos de 2 o más átomos adyacentes A_1-A_{10} son Sp3 O, S, NR^x, CR^xR^y, o C=(O ó S), con la condición que oxígeno y azufre no pueden estar adyacentes. Los restantes A_1-A_8 son CR^x ó N, y A_9 y A_{10} son carbono;

cuando n es mayor que o igual a 0, y m mayor que o igual a 0, átomos separados por 2 átomos (es decir, A_1 y A_4) son Sp3 O, S, NR^x, CR^xR^y, y los restantes A_1-A_8 son independientemente CR^x ó N, y A_9 y A_{10} son carbono.

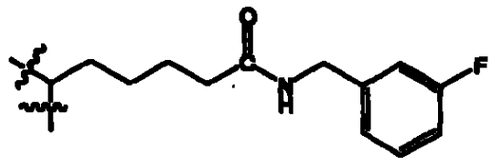
[00034] El término "sulfonilo", si se usa solo o vinculado a otros términos tales como alquilsulfonilo, denota respectivamente radicales divalentes -

SO_2-. "Alquilsulfonilo" abarca radicales alquilo unidos a un radical sulfonilo, donde alquilo de define como más arriba. El término "arilsulfonilo" abarca radicales sulfonilo sustituidos con un radical arilo. Los términos "sulfamilo" o "sulfonamidilo", solos o empleados con términos tales como "N-alquilsulfamilo", "N-arilsulfamilo", "N,N-dialquilsulfamilo" y "N-alquil-N-arilsulfamilo", denota un radical sulfonilo sustituido con un radical amina, formando una sulfonamida (-SO_2-NH_2), que puede denominarse igualmente un "aminosulfonilo". Los términos "N-alquilsulfamilo" y "N,N-dialquilsulfamilo" denotan radicales sulfamilo sustituidos, respectivamente, con un radical alquilo, un anillo cicloalquilo, o dos radicales alquilo. Los términos "N-arilsulfamilo" y "N-alquil-N-arilsulfamilo" denotan radicales sulfamilo sustituidos, respectivamente, con un radical arilo, y un radical alquilo y uno arilo. Los términos "carboxi" o "carboxilo", usados solos o con otros términos, tales como "carboxialquilo", denota -CO_2-H. El término "carboxialquilo" abarca radicales que tienen un radical carboxi como se define más arriba, unido a un radical alquilo. El término "carbonilo", usado solo o con otros términos, tales como "alquilcarbonilo", denota - (C=O) -. El término "alquilcarbonilo" abarca radicales que tienen un radical carbonilo sustituido con un radical alquilo. Un ejemplo de un radical "alquilcarbonilo" es CH_3 - (CO) -. El término "alquilcarboniloalquilo" denota un radical alquilo sustituido con un radical "alquilcarbonilo". El término "alcoxicarbonilo" significa un radical que contiene un radical alcoxi, como se define más arriba, unido por un átomo de oxígeno a un radical carbonilo (C=O). Ejemplos de tales radicales "alcoxicarbonilo" incluyen $(CH_3)_3$-C-O-C=O) - y - (O=)C- OCH_3. El término "alcoxicarboniloalquilo" abarca radicales que tienen "alcoxicarbonilo", como se define más arriba sustituido por un radical alquilo. Ejemplos de tales radicales "alcoxicarboniloalquilo" incluyen (CH_3)3C-OC(=O)-$(CH_2)_2$ - y -$(CH_2)_2$ (-O)$COCH_3$. Los términos "amido", o "carbamilo", cuando se usan solos o con otros términos tales como "amidoalquilo", "N-monoalquilamido", "N-monoarilamido", "N,N-dialquilamido", "N-alquil-N-arilamido", "N-alquil-N-hidroxiamido" y "N-

alquil-N-hidroxiamidoalquilo", abarca un radical carbonilo sustituido con un radical amino. Los términos "N-alquilamido" y "N,N-dialquilamido" denotan grupos amido que se han sustituido con un radical alquilo y con dos radicales alquilo, respectivamente. Los términos "N-monoarilamido" y "N-alquil-N-arilamido" denotan radicales amido sustituidos, respectivamente, con un radical arilo, y un radical alquilo y uno arilo. El término "N-alquil-N-hidroxiamido" abarca radicales amido sustituidos con un radical hidroxilo y con un radical alquilo. El término "N-alquil-N-hidroxiamidoalquilo" abarca radicales alquilo sustituidos con un radical N-alquil-N-hidroxiamido. El término "amidoalquilo" abarca radicales alquilo sustituidos con radicales amido. El término "aminoalquilo" abarca radicales alquilo sustituidos con radicales amino. El término "alquilaminoalquilo" abarca radicales aminoalquilo que tienen el átomo de nitrógeno sustituido con un radical alquilo. El término "amidino" denota un radical -C(-NH)-NH_2. El término "cianoamidina" denota un radical -C(-N-CN) -NH_2. El término "heterocicloalquilo" abarca radicales alquilo heterocíclico-sustituidos tales como piridilmetilo y tienilmetilo. Los términos "aralquilo", o "arilalquilo" abarcan radicales alquilo arilo-sustituidos tales como radicales alquilo tales como bencilo, difenilmetilo, trifenilmetilo, fenetilo, y difenetilo. Los términos bencilo y fenilmetilo don intercambiables. El término "cicloalquilo" abarca radicales que tienen tres a diez átomos de carbono, tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y cicloheptilo. El término "cicloalquenilo" abarca radicales insaturados que tienen tres a diez átomos de carbono, tales como ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, y cicloheptenilo. El término "alquiltio" abarca radicales que contienen un radical alquilo lineal o ramificado, de uno a diez átomos de carbono, unidos a un átomo de azufre divalente. Un ejemplo de "alquiltio" es metiltio, (CH_3 -S-). El término "alquilsulfinilo" abarca radicales que contienen un radical alquilo lineal o ramificado, de uno a diez átomos de carbono, unidos a un átomo -S(-O)- divalente. Los términos "N-alquilamino" y "N,N-dialquilamino" denotan grupos amino que se han sustituido con un radical

alquilo y con dos radicales alquilo, respectivamente. El término "acilo", usado solo o dentro de un término tal como "acilamino", denota un radical provisto por el residuo después del retiro de hidroxilo de un ácido orgánico. El término " acilamino" abarca un radical amino sustituido con un grupo acilo. Un ejemplo de un radical "acilamino" es acetilamino (CH_3-C(=O) -NH-).

[00035] En la denominación de grupos sustituyentes para estructuras químicas generales, la designación de los componentes químicos del grupo va típicamente del grupo terminal hacia el compuesto original, a menos que se anote lo contrario, como se discute más adelante. En otras palabras, la estructura químia más extrema se nombra primero, seguida por la siguiente estructura en línea, seguida por la siguiente, etc., hasta que se denomine la estructura que se conecta a la estructura principal. Por ejemplo, un grupo sustituyente que tenga una estructura tal como:



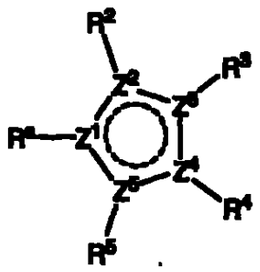
puede designarse generalmente como un "haloarilalquilaminocarboxilalquilo". Un ejemplo de un grupo tal sería fluorofenilmetilcarbamilpentilo. Los enlaces que tienen líneas onduladas a través de ellos representan la estructura principal a la cual se une el alquilo.

[00036] Igualmente grupos sustituyentes pueden nombrarse por referencia a uno o más grupos "R". La estructura indicada más arriba estaría incluida en una descripción, tal como, "-C_1-C_6-alquil-COR^u", donde R^u se define para incluir -NH-C_1-C_4-alquilaril-R^y, y donde R^y se define para incluir halo. En este esquema, átomos que tienen un grupo "R" se muestran con el grupo "R" siendo el grupo terminal (*es decir*, el más alejado del principal). En un término tal como "$C(R^x)_2$", debe entenderse que los dos grupos R^x pueden ser los mismos, o pueden ser diferentes si R^x se define como teniendo más de una identidad posible.

[00037] La presente invención comprende además compuestos inhibidores

de MK-2 que tienen la estructura mostrada en la fórmula II:

Fórmula II.

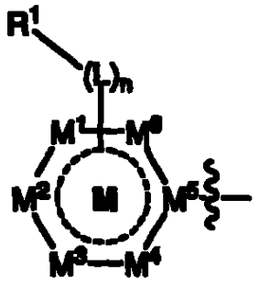


en donde:

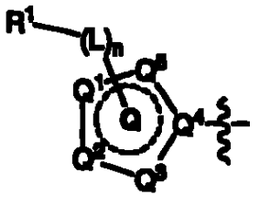
Z^2 y Z^3 son nitrógeno, Z^1, Z^4 y Z^5 son carbono, y se juntan con Z^2 y Z^3 para formar un anillo pirazol, o de manera opcional, Z^4 y Z^5 son nitrógeno, Z^1, Z^2 y Z^3 son carbono y se juntan con Z^4 y Z^5 para formar un anillo pirazol;

R^a se selecciona de:

1)



2)



, y

3)



donde las líneas discontinuas indican enlaces simples o dobles opcionales;

cuando R^a es anillo M y anillo M es aromático, M^1 es carbono y es sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono y nitrógeno y es no sustituido o sustituido con $(L)_nR^1$;

cuando anillo M es parcialmente saturado, M^1 es carbono y es mono- o di-sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y cuando M^2, M^3, M^4, o M^6 es oxígeno o azufre, es no sustituido, y cuando M^2, M^3, M^4 o M^6 es carbono o nitrógeno, es opcionalmente no sustituido; o mono- o di-sustituido con $(L)_nR^1$;

cuando R^a es anillo Q y anillo Q es aromático, Q^1 se selecciona de carbono y nitrógeno, y cuando Q^1 es carbono, se sustituye con $(L)_nR^1$, y cuando Q^1 es nitrógeno, es no sustituido, Q^4 se selecciona de nitrógeno y carbono, y cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

opcionalmente, cuando anillo Q es aromático, Q^1 es carbono y es sustituido con $(L)_nR^1$, Q^4 es carbono, y uno de Q^2, Q^3 y Q^5 es opcionalmente oxígeno o azufre, y el resto de Q^2, Q^3 y Q^5 se seleccionan independientemente de nitrógeno y carbono, y si carbono, se sustituyen con $(L)_nR^1$;

cuando anillo Q es parcialmente saturado, Q^1 se selecciona de carbono y nitrógeno, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$, Q^4 se selecciona de carbono y nitrógeno, pero sólo uno de Q^1 y Q^4 puede ser nitrógeno, cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y si oxígeno o azufre, es no sustituido, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$;

cuando R^a es estructura 3, es completamente conjugado, X^2 se selecciona de oxígeno o nitrógeno sustituido con $(L)_nR^1$, X^1 es carbono y es sustituido con $(L)_nR^1$, y cada uno de X^5 y X^6 se selecciona independientemente de nitrógeno y carbono, y si carbono, se sustituye con

$(L)_nR^1$;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, hidroxilo, C_1-C_6 alcoxi, C_2-C_6 alquenil-R^{11}, C_1-C_6 alcoxi-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alquilo, hidroxi C_1-C_4 alquilo, amino, amino C_1-C_4 alquil-R^7, C_1-C_6 alquil-NHR^7, carbonitrilo, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_6 alquilo, NR^8R^9-C_1-C_6 alquilo, nitro, ciano, O-R^{10}, C_1-C_4 alquil-OR^{10}, C_1-C_6 alquil-COR^{11}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, o C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{12};

R^7 y R^8 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, arilo, y arilalquilo, en donde arilo y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^9 y R^{10} se seleccionan cada uno independientemente de -H, hidroxilo, C_1-C_6 alquilo, C_1-C_6 alquil-R^{17}, C_1-C_6 alquil-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alquil-CO_2R^{16}, C_1-C_6 alquil-$CONH$-R^{16}, C_1-C_6 alquil-$CON(R^{16})_2$, hidroxi C_1-C_4 alquilo, halo C_1-C_4 alcoxi, halo C_1-C_4 alquilo, $Si(R^{13})_2R^{17}$, arilo, heteroarilo, heterociclilo, arilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxilo, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo, y heterociclilalquilo, en donde heterociclilo, heteroarilalquilo, y heterociclilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, hidroxilo, oxo, C_1-C_6 alquilo, hidroxil C_1-C_6 alquil-R^{11}, C_1-C_{10} alcoxi, amino, amino C_1-C_4 alquil-R^7, NHR^7, $N(R^7)_2$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NHR^8R^9, C_1-C_6 alquil-$N(R^8)_2$, C_1-C_6 alquil-

R^{11}, C_1-C_6 alquil-$CO_2R^7R^{11}$, C_1-C_6 alcoxi-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_6 alquil-SR^{10}, halo, halo C_1-C_4 alquilo, halo C_1-C_4 alcoxi, hidroxi C_1-C_4 alquilo, hidroxi C_1-C_4 alcoxi, arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, y heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{13} y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, COR^{23}, y arilo;

R^{15} y R^{16} se seleccionan cada uno independientemente de -H, arilo, arilalquilo, en donde arilo, arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alquil-R^{19}, NHR^{19}, arilo, heteroarilalquilo, y heterociclilalquilo, en donde arilo se sustituye opcionalmente con uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, hidroxilo, C_1-C_{10} alquilo, C_1-C_{10} alcoxi, amino, amino C_1-C_6 alquilo, $N(R^{19})_2$, C_1-C_6 alquil-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, y heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, heteroarilo, heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan cada uno independientemente de -H y C_1-C_6 alquilo;

R^{23} se selecciona de -H y C_1-C_6 alquilo;

R^{24} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, CO_2R^{29}, halo, y halo C_1-C_4 alquilo;

R^{29} se selecciona de -H, y C_1-C_6 alquilo;

R^{30} se selecciona de -H, arilo, heteroarilo, heterociclilo, alquilarilo,

arilalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H y halo;

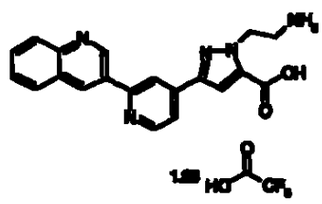
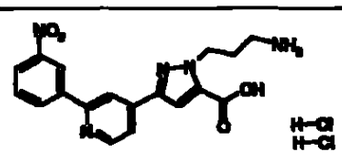
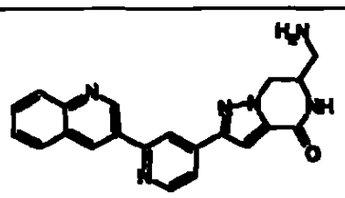
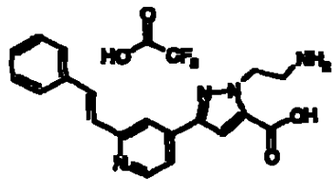
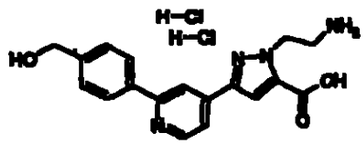
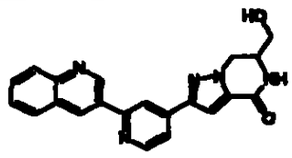
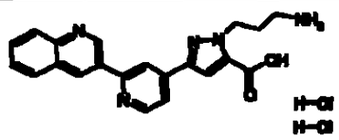
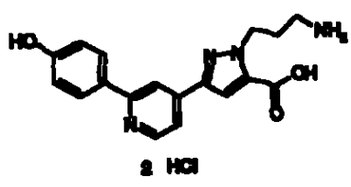
R^2, R^3, R^4, R^{37} y R^{38} se seleccionan cada uno independientemente de un grupo R^1;

n es 0; y

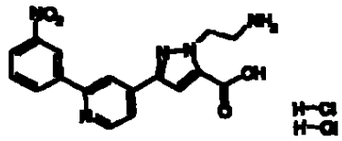
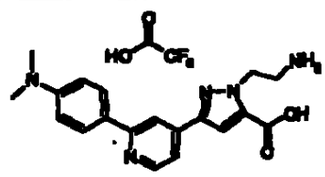
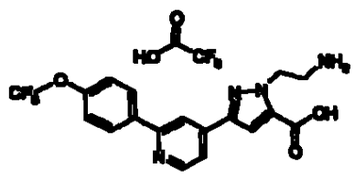
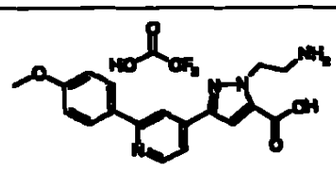
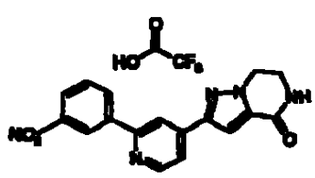
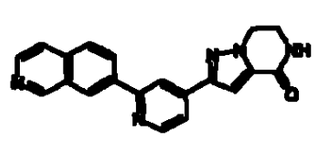
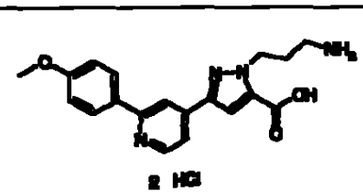
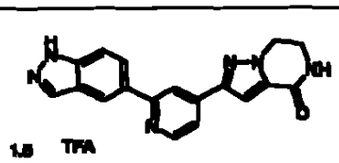
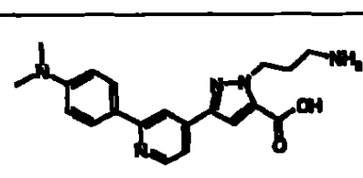
R^3 y R^4 se juntan de manera opcional para formar un anillo de 5, 6, 7, u 8 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

[00038] Tabla I y Tabla II muestran ejemplos de compuestos inhibidores de MK-2 de la presente invención, e indican asimismo el nombre químico y, donde se encuentra disponible, el valor IC_{50} del compuesto para la inhibición de MK-2. Se cree que cualquiera de los compuestos, enumerados en la Tabla I y Tabla II con compuestos inhibidores de MK-2, puede usarse en el método de la presente invención. No obstante, ni los novedosos compuestos inhibidores de MK-2, ni los usos de un compuesto inhibidor de MK-2, descritos aquí, tienen como finalidad limitarse a los compuestos que se presentan en las siguientes Tablas.

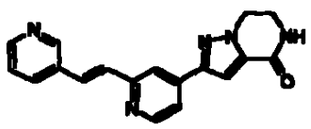
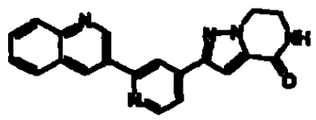
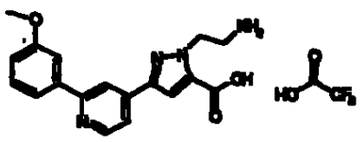
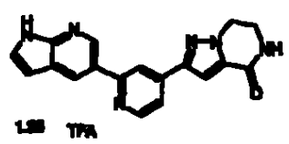
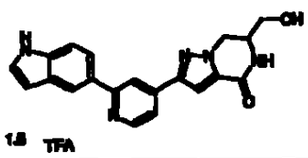
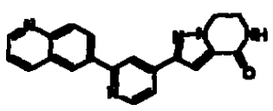
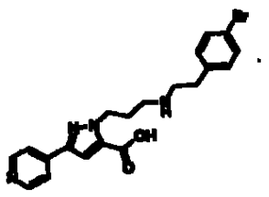
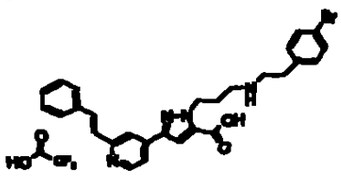
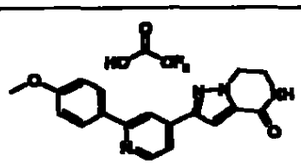
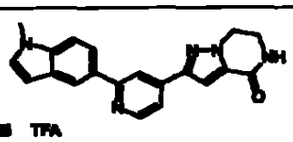
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Tabla I: Compuestos Inhibidores de MK-2			
No.	Estructura	Nombre del Compuesto (a)[b]	IC_{50} Promedio MK-2 (uM)
1		trifluoroacetato de ácido 1-(2-aminoetil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxílico	0.0269
2		diclorhidrato de ácido 1-(3-aminopropil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxílico	0.0397
3		6-(aminometil)-2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.0477
4		trifluoroacetato de ácido 1-(2-aminoetil)-3-[2-[(E)-2-feniletenil]piridin-4-il]-1H-pirazol-5-carboxílico	0.0505
5		diclorhidrato de ácido 1-[2-aminoetil)-3-[2-[4-(hidroximetil)fenil]piridin-4-il]-1H-pirazol-5-carboxílico	0.0533
6		6-(hidroximetil)-2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.0615
7		diclorhidrato de ácido 1-(3-aminopropil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxílico	0.0686
8		clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxílico	0.102

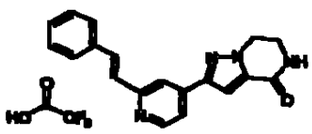
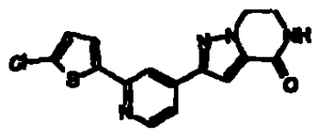
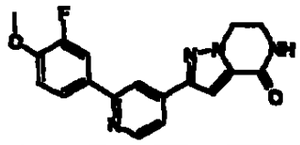
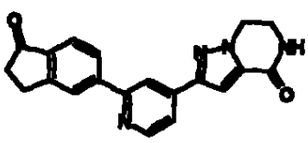
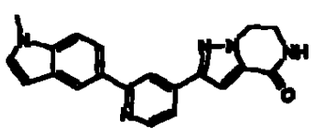
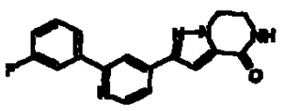
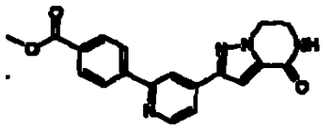
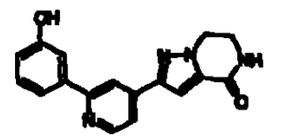
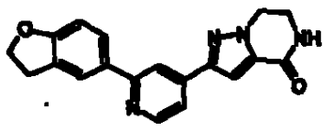
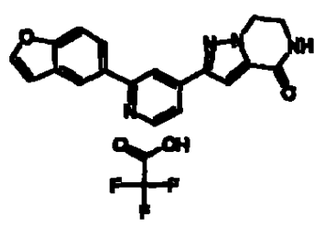
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9		diclorhidrato de ácido 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxílico	0.109
10		trifluoroacetato de ácido 1-(2-aminoetil)-3-{2-[4-(dimetilamino)fenil]piridin-4-il}-1H-pirazol-5-carboxílico	0.117
11		trifluoroacetato de ácido 1-(2-aminoetil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxílico	0.161
12		trifluoroacetato de ácido 1-(2-aminoetil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5 carboxílico	0.168
13		trifluoroacetato de 2-[2-(3-nitrofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.171
14		2-(2-isoquinolin-7-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.194
15	 2 HCl	clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico	0.196
16	 1,5 TFA	trifluoroacetato de 2-[2-(1H-indazol-5-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.199
17	 2 HCl	clorhidrato de ácido 1-(3-aminopropil)-3-{2-[4-dimetilamino)fenil]piridin-4-il}-1H-pirazol-5-carboxílico	0.203

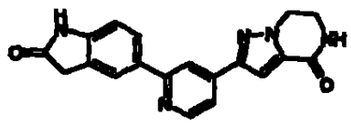
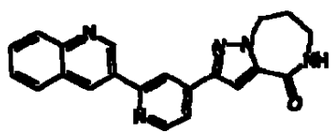
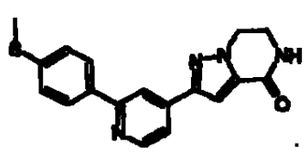
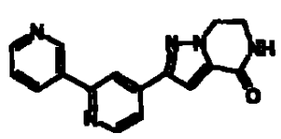
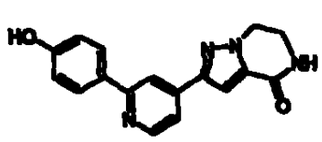
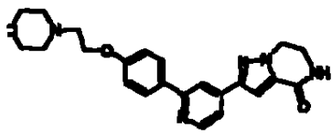
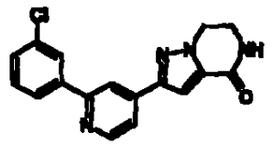
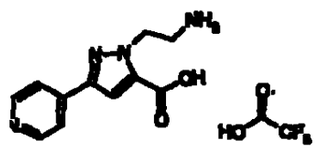
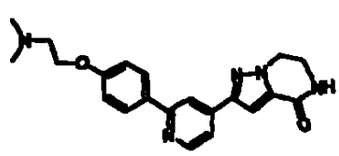
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18		2-[2-[(E)-2-piridin-3-iletenil]piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.212
19		2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.216
20		trifluoroacetato de ácido 1-(2-aminoetil)-3-[2-(3-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico	0.217
21		trifluoroacetato de 2-[2-(1H-pirrolo[2,3-b]piridin-5-il)piridin-4 il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.226
22		trifluoroacetato de 6-(hidroximetil)-2-[2-(1 H-indol-5-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.25
23		2-(2-quinolin-6-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.298
24		clorhidrato de ácido 1-(3-{[2-(4-bromofenil)etil]amino}propil)-3-piridin-4-il-1H-pirazol-5-carboxílico	0.3
25		trifluoroacetato de ácido 1-(3-{[2-(4-bromofenil)etil]amino}propil)-3-{2-[(E)-2-feniletenil]piridin-4-il}-1H-pirazol-5 carboxílico	0.315
26		trifluoroacetato de 2-[2-(4-metoxifenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	0.318
27		trifluoroacetato de 2-[2-(1-metil-1H-indol-5-il) piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	0.322

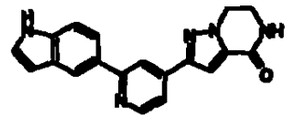
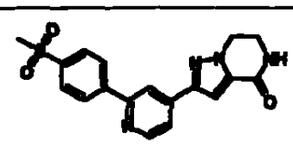
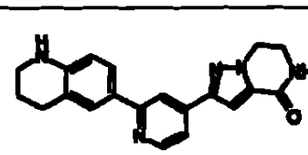
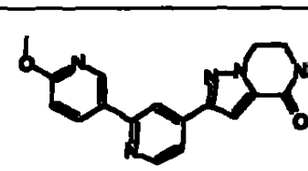
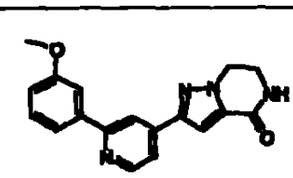
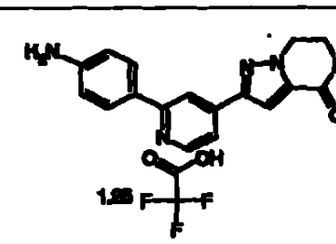
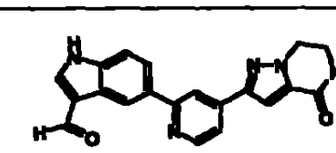
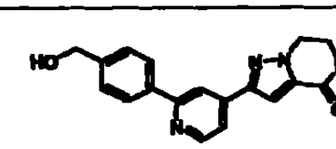
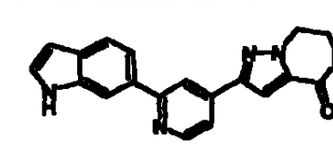
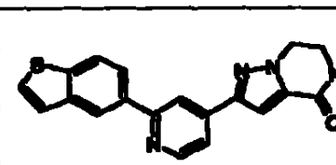
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28		trifluoroacetato de 2-[2-[(E)-2-fenilvinil]piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	0.371
29		2-[2-(5-clorotien-2-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	0.444
30		2-[2-(3-fluoro-4-metoxifenil) piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	0.471
31		2-[2-(1-oxo-2,3-dihidro-1H-inden-5-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.478
32		2-[2-[1-metil-1H-indol-5-il) piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.479
33		2-[2-(3-fluorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.505
34		metil 4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)piridin-2-il]benzoato	0.511
35		2-[2-(3-hidroxifenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.52
36		2-[2-(2,3-dihidro-1-benzofuran-5-il) piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	0.521
37		trifluoroacetato de 2-[2-(1-benzofuran-5-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	0.543

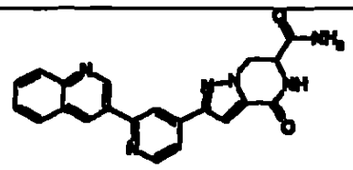
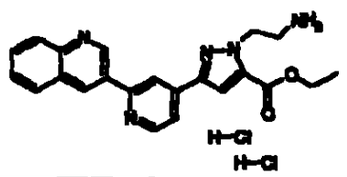
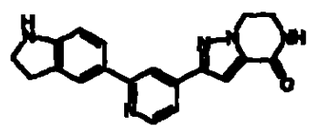
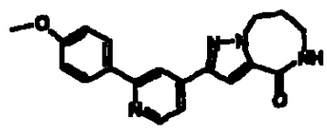
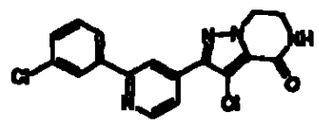
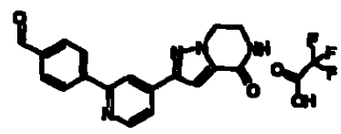
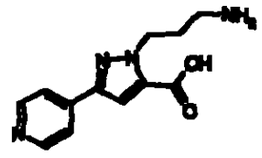
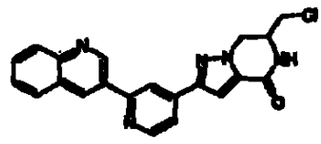
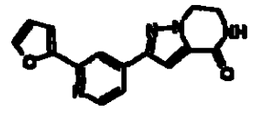
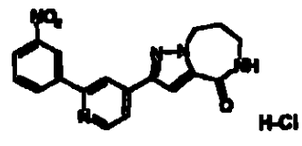
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38		2-[2-(2-oxo-2,3-dihidro-1H-indol-5-il)piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	0.554
39		2-(2-quinolin-3-ilpiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	0.577
40		2-[2-[4-(metiltio)fenil]piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.581
41		2-(2,3'-bipiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.586
42		2-[2-(4-hidroxifenil)piridin-4-il]-6,7-dihidropirazolo(1,5-a]pirazin-4(5H)-ona	0.611
43		2-[2-[4-(2-morfolin-4-iletoxi)fenil]piridin-4-il]6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.63
44		2-[2-(3-clorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.638
45		trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol 5-carboxílico	0.735
46		2-(2-[4-[2-[dimetilamino)etoxi] fenil)piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.766

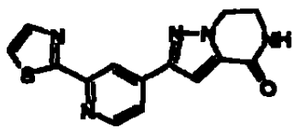
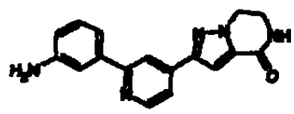
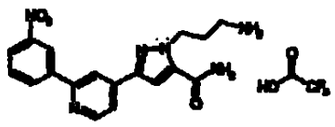
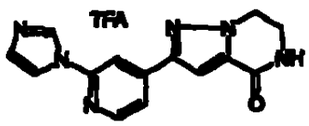
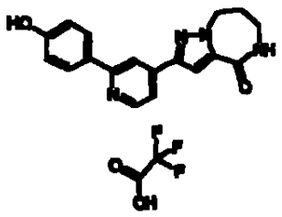
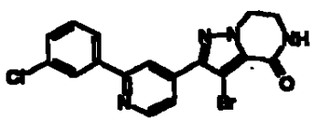
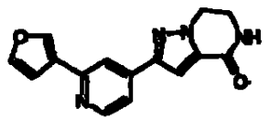
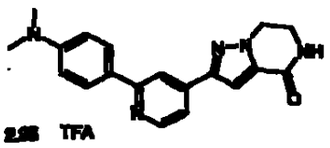
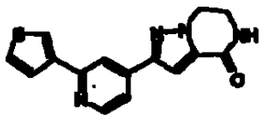
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47		2-[2-(1H-indol-5-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.808
48		2-(2-[4-(metilsulfonil)fenil] piridin-4-il}-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	0.821
49		2-[2-(1,2,3,4-tetrahidroquinolin-6-il)piridin 4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.835
50		2-(6'-metoxi-2,3'-bipiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.866
51		2-[2-(3-metoxifenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	0.906
52		trifluoroacetato de 2-[2-(4-aminofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.914
53		5-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)piridin-2-il]-1H-indol-3-carbaldehído	0.923
54		2-[2-[4-(hidroximetil)fenil] piridin-4-il}-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	0.929
55		2-[2-(1H-indol-6-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	0.93
56		2-[2-(1-benzotien-5-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	0.965

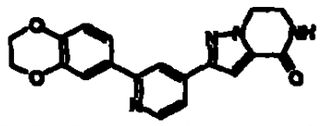
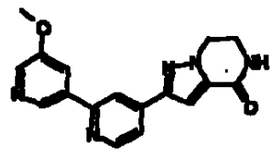
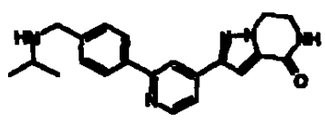
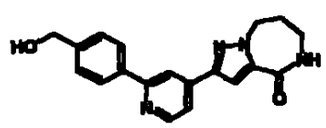
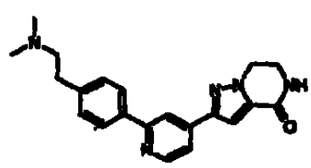
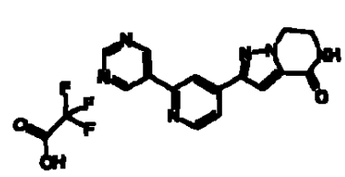
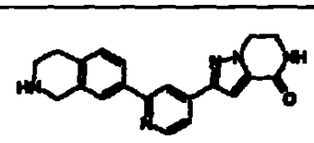
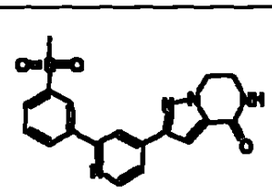
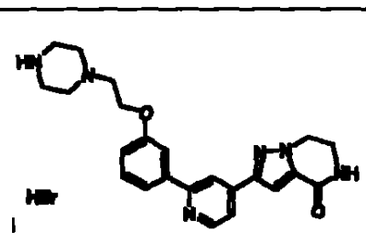
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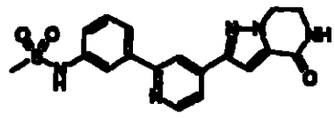
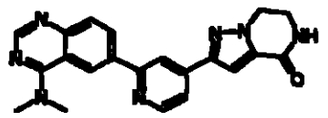
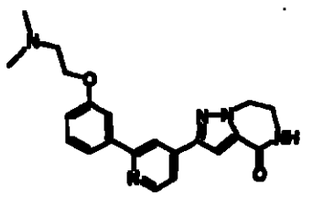
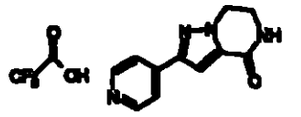
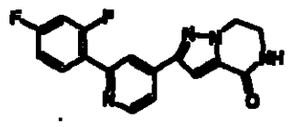
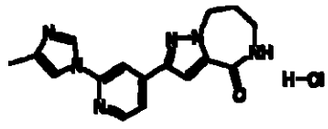
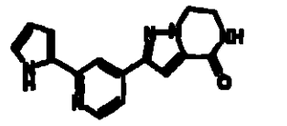
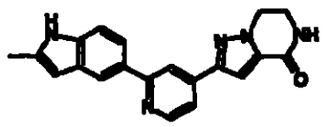
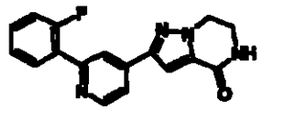
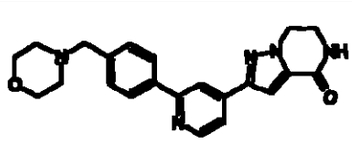
57		4-oxo-2-(2-quinolin-3-ilpiridin-4-il)-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-6-carboxamida	1.01
58		diclorhidrato de etil 1-(2-aminoetil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato	1.03
59		2-[2-(2,3-dihidro-1H-indol-5-il)piridin-4-il]-6,7-dihidropirazolo(1,5-a]pirazin-4(5H)-ona	1.07
60		2-[2-(4-metoxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo [1,5-a][1,4]diazepin-4-ona	1.09
61		3-cloro-2-[2-(3-clorofenil) piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	1.13
62		trifluoroacetato de 4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)piridin-2-il]benzaldehído	1.15
63		ácido 1-(3-aminopropil)-3-piridin-4-il-1H-pirazol-5-carboxílico	1.16
64		13012 o 6-(clorometil)-2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.17
65		2-[2-(2-furil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.2
66		clorhidrato de 2-[2-(3-nitrofenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	1.26

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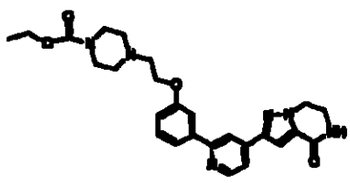
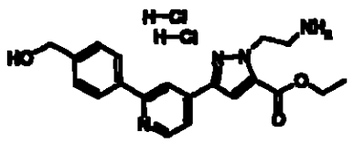
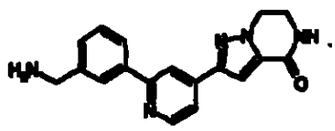
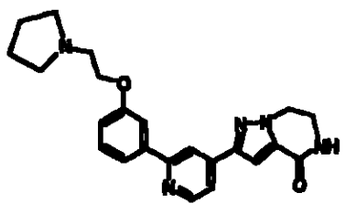
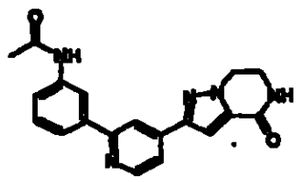
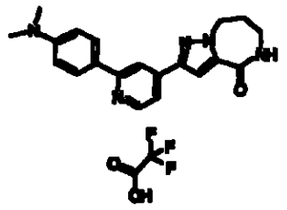
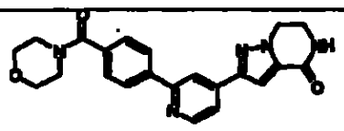
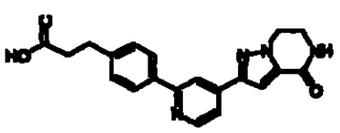
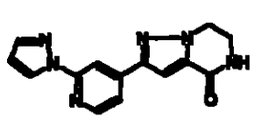
67		2-[2-(1,3-tiazol-2-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.29
68		2-[2-(3-aminofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.3
69		trifluoroacetato de 1-(3-aminopropil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxamida	1.32
70		trifluoroacetato de 2-[2-(1H-imidazol-1-il)piridin-4-il]-6,7-dihidropirazolo [1,5-a] pirazin-4(5H)-ona	1.36
71		trifluoroacetato de 2-[2-(4-hidroxifenil]piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a] [1,4]diazepin-4-ona	1.37
72		3-bromo-2-[2-(3-clorofenil) piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	1.39
73		2-[2-(3-furil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.46
74		trifluoroacetato de 2-{2-[4-(dimetilamino)fenil] piridin-4-il)-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	1.53
75		2-(2-tien-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.55

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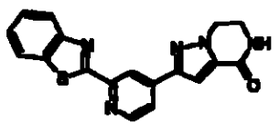
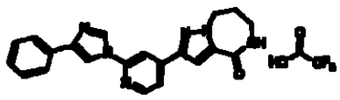
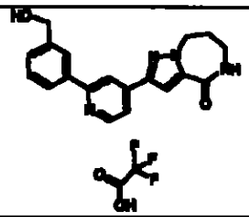
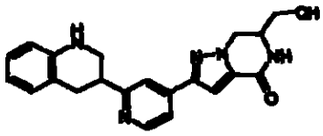
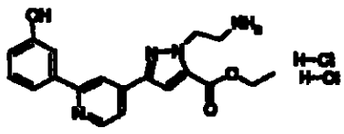
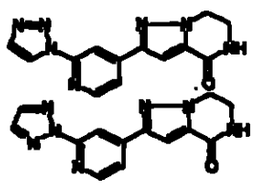
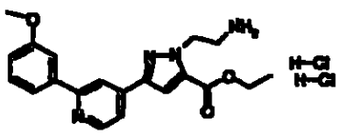
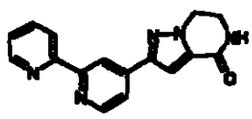
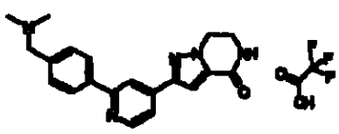
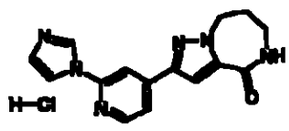
76		2-[2-(2,3-dihidro-1,4-benzodioxin-6-il)piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	1.56
77		2-(5'-metoxi-2,3'-bipiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.69
78		2-(2-{4-[(isopropilamino)metil] fenil}piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.73
79		2-{2-[4-(hidroximetil)fenil] piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	1.75
80		2-(2-{4-[2-(dimetilamino)etil] fenil)piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.98
81		trifluoroacetato de 2-(2-pirimidin-5-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	1.99
82		2-[2-(1,2,3,4-tetrahidroisoquinolin-7-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	2.08
83		2-{2-[3-(metilsulfonil)fenil] piridin-4-il}-6,7-dihidropirazolo) [1,5-a]pirazin-4(5H)-ona	2.1
84		hidrobromuro de 2-{2-[3-(2-piperazin-1-iletoxi) fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	2.13

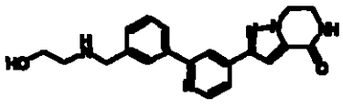
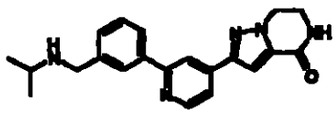
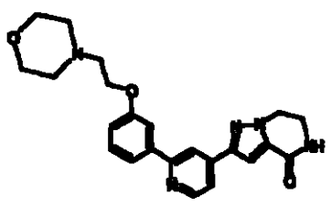
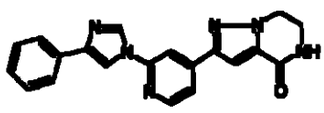
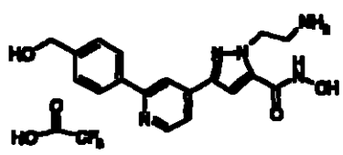
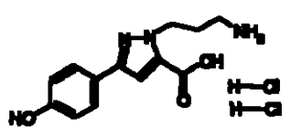
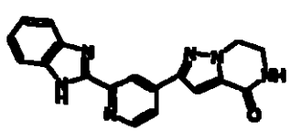
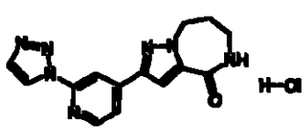
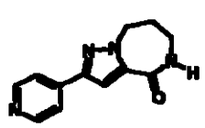
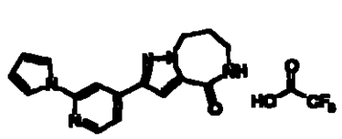
85		N-[3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) piridin-2-il]fenil}metanosulfonamida	2.29
86		2-[2-[4-(dimetilamino)quinazolin-6-il]piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	2.4
87		2-(2-{3-[2-(dimetilamino)etoxi] fenil}piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	2.4
88		trifluoroacetato de 2-piridin-4-il-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	2.6
89		2-[2-(2,4-difluorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	2.62
90		clorhidrato de 2-[2-(4-metil-1H-imidazol-1-il) piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	2.76
91		2-[2-(1H-pirrol-2-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	2.79
92		2-[2-(2-metil-1H-indol-5-il) piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	2.83
93		2-[2-(2-fluorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	2.95
94		2-{2-[4-(morfolin-4-ilmetil) fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	2.99

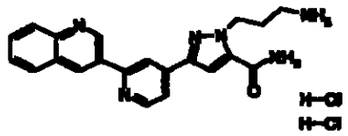
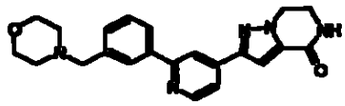
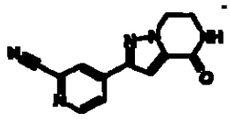
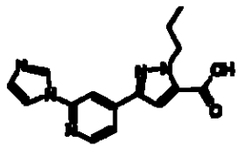
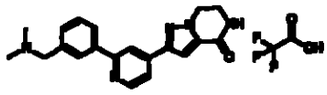
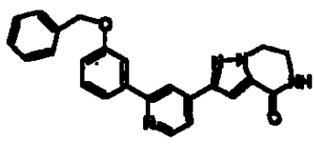
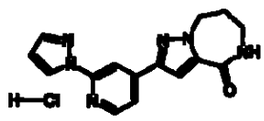
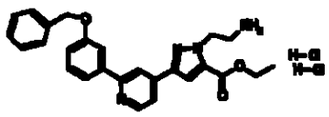
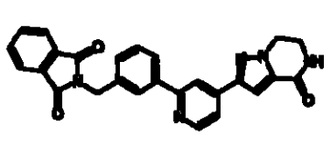
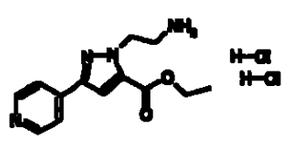
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95		etil 4-(2-{3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)piridin-2-il]fenoxi}etil) piperazin-1-carboxilato	3.02
96		diclorhidrato de etil 1-(2-aminoetil)-3-[2-[4-(hidroximetil)fenil]piridin-4-il]-1H-pirazol-5-carboxilato	3.25
97		2-[2-[3-(aminometil)fenil] piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	3.25
98		2-[2-[3-[2-pirrolidin-1-iletoxi) fenil]piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	3.27
99		N-{3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) piridin-2-il]fenil}acetamida	3.31
100		trifluoroacetato de 2-[2-[4-(dimetilamino)fenil]piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	3.44
101		2-[2-[4-(morfolin-4-ilcarbonil)fenil]piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	3.65
102		ácido 3-[4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) piridin-2-il]fenil)propanoico	4.19
103		2-[2-(1H-pirazol-1-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	4.2

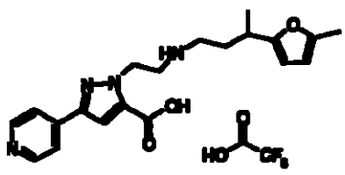
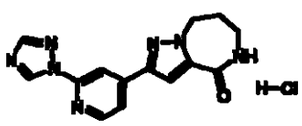
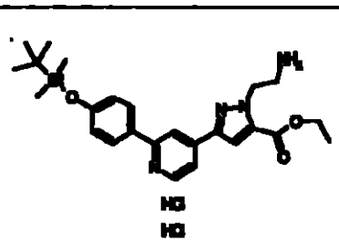
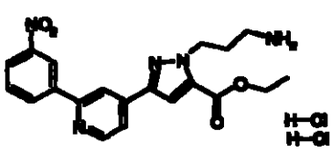
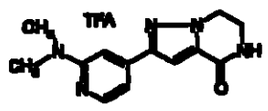
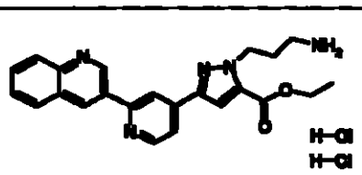
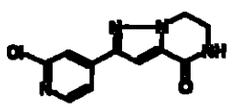
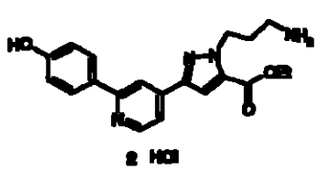
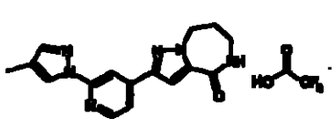
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104		2-[2-(1,3-benzotiazol-2-il)piridin-4-il-6,7-dihidropirazola[1,5-a]pirazin-4(5H)-ona	4.27
105		trifluoroacetato de 2-[2-(4-fenil-1H-imidazol-1-il) piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	4.31
106		trifluoroacetato de 2-[2-[3-(hidroximetil)fenil]piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo [1,5-a][1,4]diazepin-4-ona	4.54
107		6-(hidroximetil)-2-[2-(1,2,3,4-tetrahidroquinolin-3-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	4.9
108		diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxilato	4.98
109		compuesto de 2-[2-(2H-1,2,3-triazol-2-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona con 2-[2-(1H-1,2,3-triazol-1-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona (1:1)	5.21
110		diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato	5.23
111		2-(2,2'-bipiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	5.34
112		trifluoroacetato de 2-(2-(4-[(dimetilamino)metil] fenil}piridin-4-il 6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	5.35
113		clorhidrato de 2-[2-(1H-imidazol-1-il)piridin-4-il]-5, 6, 7, 8-tetrahidro-4H-pirazolo[1, 5-a] [1, 4] diazepin-4-ona	5.66

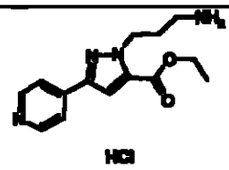
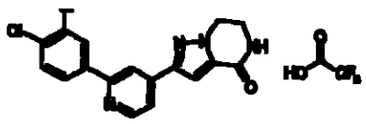
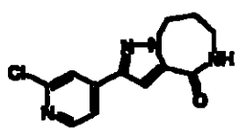
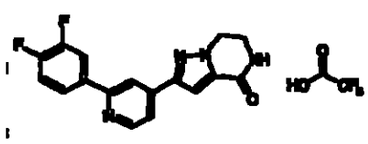
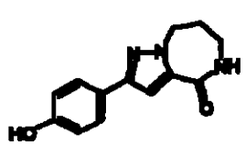
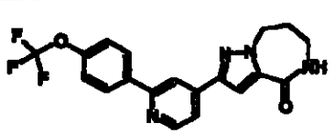
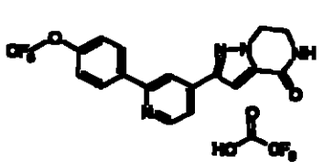
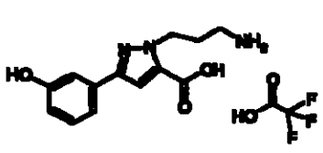
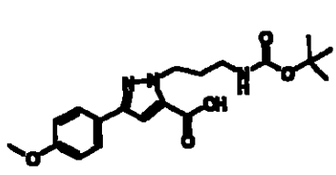
114		2-[2-(3-[[(2-hidroxietil)amino] metil}fenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	5.78
115		2-(2-{3-[(isopropilamino)metil] fenil)piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	6.27
116		2-{2-[3- (2-morfolin-4-iletoxi) fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	6.73
117		2-[2-(4-fenil-1H-imidazol-1-il) piridin-4-il]-6,7-dihidropirazolo [1,5-a] pirazin-4 (5H)-ona	7.04
118		trifluoroacetato de 1-(2-aminoetil)-N-hidroxi-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxamida	7.91
119		diclorhidrato de ácido 1-(3-aminopropil)-3-(4-hidroxifenil)-1H-pirazol-5-carboxílico	8.11
120		2-[2-(1H-benzimidazol-2-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4 (5H)-ona	8.92
121		clorhidrato de 2-[2-(1H-1,2,3-triazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a] [1,4]diazepin-4-ona	9.05
122		2-piridin-4-il-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	10.1
123		trifluoroacetato de 2-[2-(1H-pirrol-1-il)piridin-4-il]-5,6,7, 8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	10.6

124		diclorhidrato de 1-(3-aminopropil)-3-(2-quinolin-3-il)piridin-4-il)-1H-pirazol-5-carboxamida	10.7
125		2-[2-[3-(morfolin-4-ilmetil)fenil] piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	11.4
126		4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)piridin-2-carbonitrilo	13.8
127		ácido 3-[2-(1H-imidazol-1-il)piridin-4-il]-1-propil-1H-pirazol-5-carboxílico	14.3
128		trifluoroacetato de 2-(2-{3-[(dimetilamino)metil] fenil}piridin-4-il)6,7-dihidropirazolo [1,5-a] pirazin-4(5H)-ona	15.4
129		2-[2-[3-(benciloxi)fenil]piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	15.5
130		clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a] [1,4]diazepin-4-ona	16.2
131		diclorhidrato de etil 1-(2-aminoetil)-3-{2-[3-(benciloxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato	20
132		2-{3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) piridin-2-il]bencil}-1H-isoindol-1,3 (2H)-diona	20
133		diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato	24.5

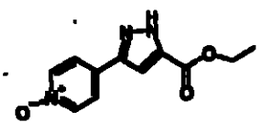
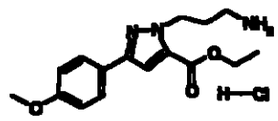
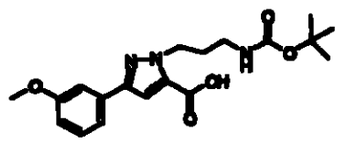
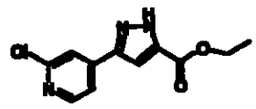
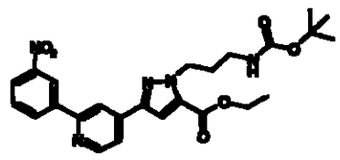
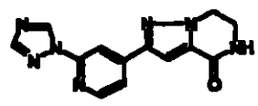
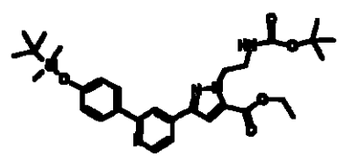
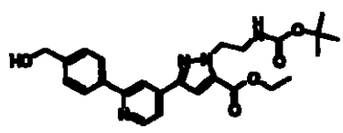
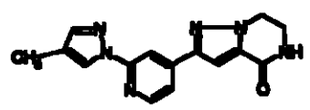
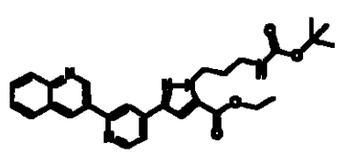
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134		trifluoroacetato de ácido 1-(2-[[3-(5-metil-2-furil)butil] amino}etil)-3-piridin-4-il-1H-pirazol-5-carboxílico	27.2
135		clorhidrato de 2-[2-(1H-1,2,4-triazol-1-il) piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	28.2
136		diclorhidrato de etil 1-(2-aminoetil)-3-[2- (4-[[terc-butil(dimetil)silil]oxi)fenil) piridin-4-il]-1H-pirazol-5-carboxilato	28.3
137		diclorhidrato de etil 1-(3-aminopropil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato	31.6
138		trifluoroacetato de 2-[2-(dimetilamino)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	37.2
139		diclorhidrato de etil 1-(3-aminopropil)-3- (2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato	38.6
140		2-(2-cloropiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	44.8
141		clorhidrato de etil 1-(3-aminopropil)-3-[2-(4-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxilato	47.5
142		trifluoroacetato de 2-[2-(4-metil-1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo [1,5-a][1,4]diazepin-4-ona	53.4

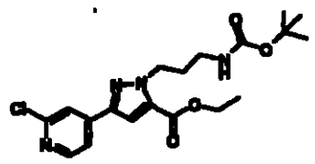
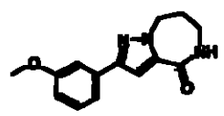
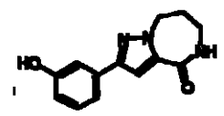
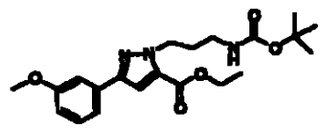
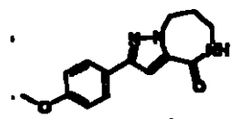
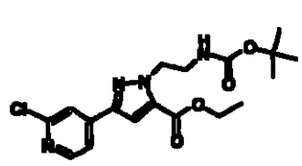
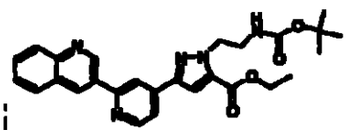
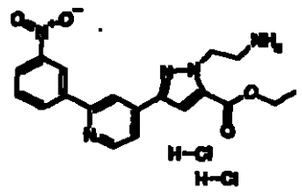
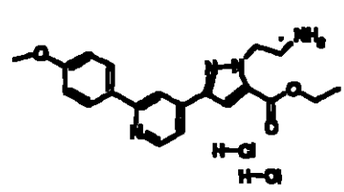
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143		clorhidrato de etil 1-(3-aminopropil)-3-piridin-4-il-1H-pirazol-5-carboxilato	60.8
144		trifluoroacetato de 2-[2-(3,4-diclorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	65.5
145		2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	80.4
146		trifluoroacetato de 2-[2-(3,4-difluorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	88.9
147		2-(4-hidroxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	118
148		2-{2-[4-(trifluorometoxi) fenil] piridin-4-il}5,6,7,8-tetrahidro-4H-pirazolo [1,5-a][1,4] diazepin-4-ona	124
149		trifluoroacetato de 2-{2-[4-(trifluorometoxi)fenil] piridin-4-il}-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	131
150		trifluoroacetato de ácido 1-(3-aminopropil)-3- (3-hidroxifenil)-1 H-pirazol-5-carboxílico	153
151		ácido 1-{3-[(terc-butoxicarbonil)amino} propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxílico	155

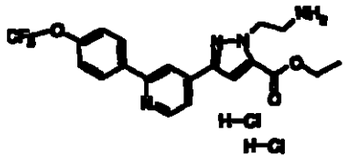
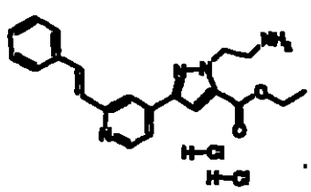
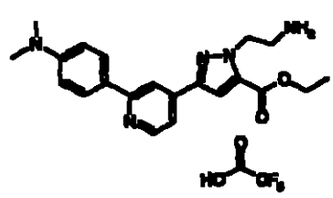
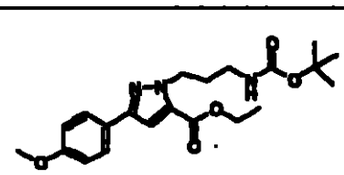
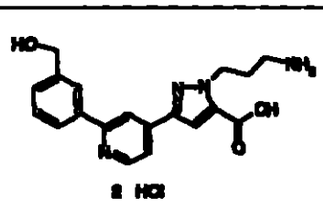
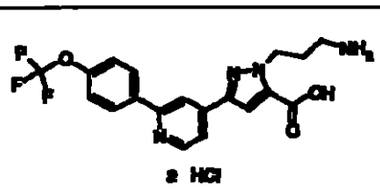
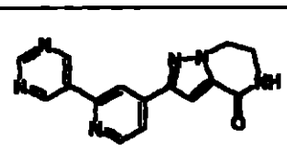
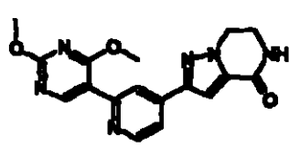
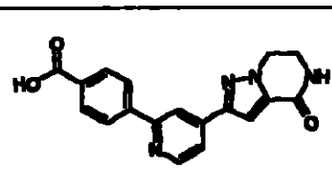
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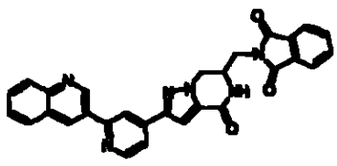
152		etil 3-(1-oxidopiridin-4-il)-1H-pirazol-5-carboxilato	200
153		clorhidrato de etil 1-(3-aminopropil)-3-(4-metoxifenil)-1H-pirazol-5-carboxilato	200
154		ácido 1-{3-[(terc-butoxicarbonil)amino] propil}-3-(3-metoxifenil)-1H-pirazol-5-carboxílico	200
155		etil 3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato	200
156		etil 1-{3-[(terc-butoxicarbonil)amino] propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato	200
157		2-[2-(1H-1,2,4-triazol-1-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4 (5H)-ona	200
158		etil 1-{2-[(terc-butoxicarbonil)amino] etil}-3-[2-(4-{[terc-butil(dimetil) silil]oxi}fenil)piridin-4-il]-1H-pirazol-5-carboxilato	200
159		etil 1-{2-[(terc-butoxicarbonil)amino] etil}-3-{2-[4-(hidroximetil)fenil] piridin-4-il}-1H-pirazol-5-carboxilato	200
160		2-[2-(4-metil-1H-pirazol-1-il)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	200
161		trifluoroacetato de 2-{2-[4-(trifluorometoxi)fenil] piridin-4-il}-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	200

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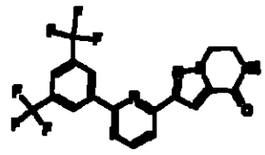
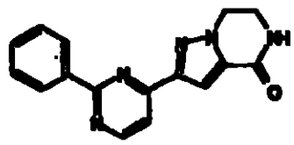
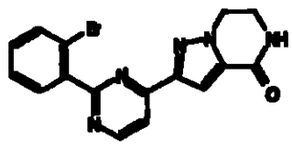
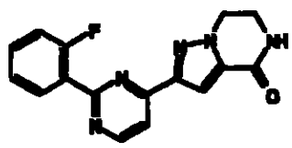
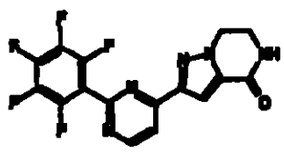
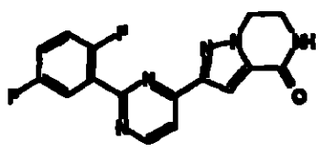
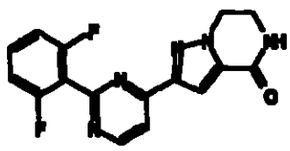
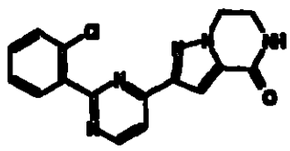
162		etil 1-{3-[(terc-butoxicarbonil)amino] propil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato	200
163		2-(3-metoxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	200
164		2-(3-hidroxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	200
165		etil 1-{3-[(terc-butoxicarbonil)amino] propil}-3-(3-metoxifenil)-1H-pirazol-5-carboxilato	200
166		2-(4-metoxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona	200
167		etil 1-[2-[(terc-butoxicarbonil)amino] etil]-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato	
168		etil 1-[2-[(terc-butoxicarbonil)amino] etil]-3-(2-quinolin-3-ilpiridin-4-il]-1H-pirazol-5-carboxilato	
169		diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5- carboxilato	
170		diclorhidrato de etil 1-(2-aminoetil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato	

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193

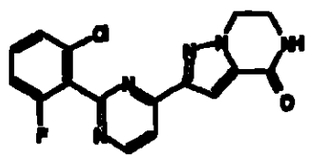
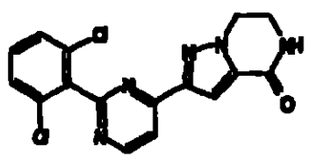
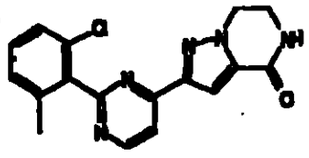
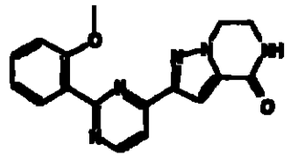
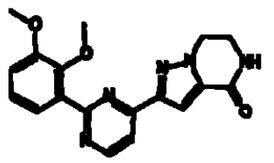
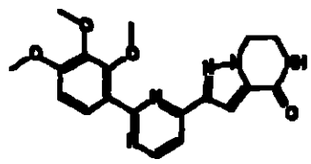
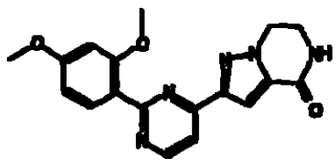
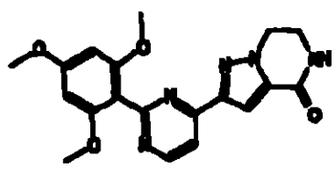
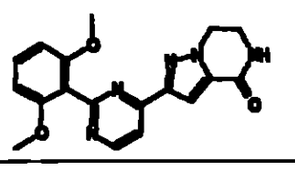
171		diclorhidrato de etil 1-(2-aminoetil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato	
172		diclorhidrato de etil 1-(2-aminoetil)-3-{2-[(E)-2-feniletenil)]piridin-4-il}-1H-pirazol-5-carboxilato	
173		trifluoroacetato de etil 1-(2-aminoetil)-3-{2-[4-(dimetilamino)fenil]piridin-4-il}-1H-pirazol-5-carboxilato	
174		etil 1-{3-[(terc- butoxicarbonil)amino] propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxilato	
175		clorhidrato de ácido 1-(3-aminopropil)-3-{2-[3-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxílico	
176		clorhidrato de ácido 1-(3-aminopropil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxílico	
177		2-(2-pirimidin-5-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
178		2-[2-(2, 4-dimetoxipirimidin-5-il) piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
179		ácido 4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)piridin-2-il]benzoico	

180		2-[[4-oxo-2-(2-quinolin-3-ilpiridin-4-il)-4,5,6,7-tetrahidropirazolo [1,5-a] pirazin-6-il]metil]-1H-isoindol-1,3(2H)-diona	

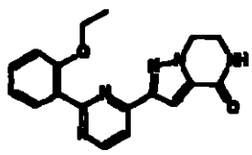
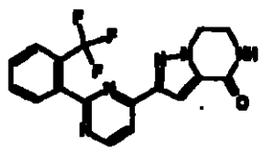
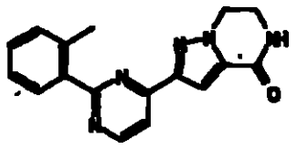
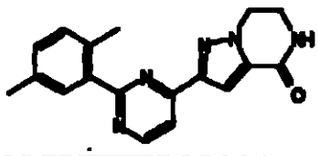
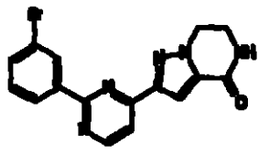
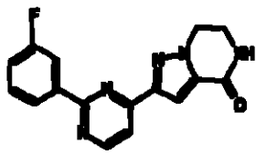
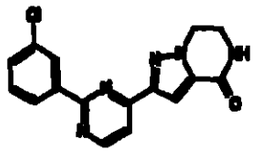
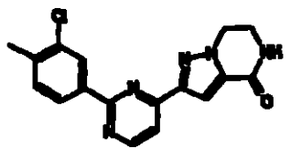
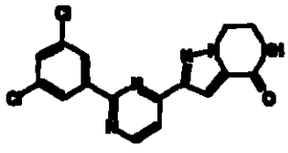
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Tabla II: Compuestos Adicionales Inhibidores de MK-2			
No.	Estructura	Nombre (s) del Compuesto b	IC_{50} Prom. MK-2 (uM)
181		2-[2-[3,5-bis(trifluorometil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
182		2-(2-fenilpirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
183		2-[2-(2-bromofenil)pirimidin-4-il]-6, 7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
184		2-[2-(2-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
185		2-[2-(pentafluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
186		2-[2-(2,5-difluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
187		2-[2-(2,6-difluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
188		2-[2-(2-clorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

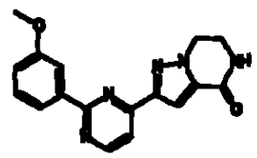
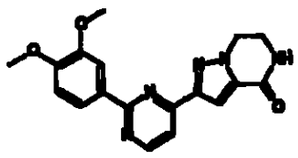
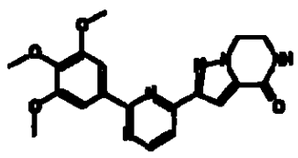
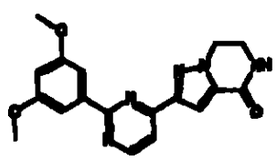
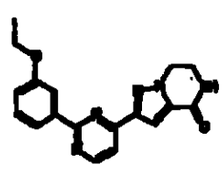
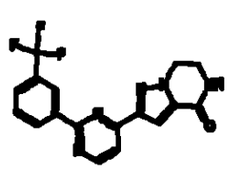
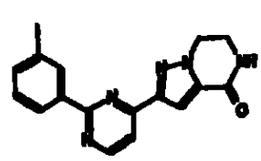
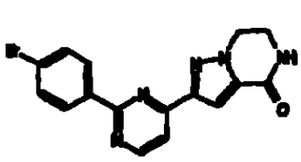
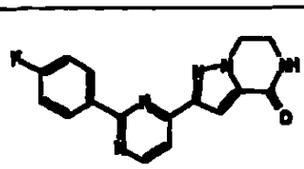
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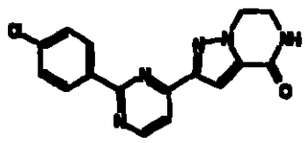
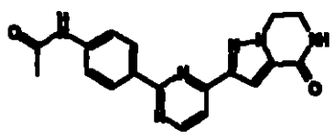
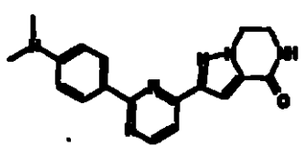
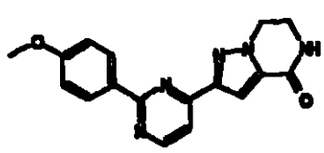
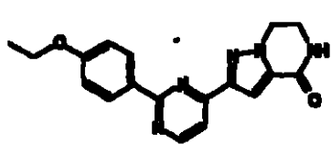
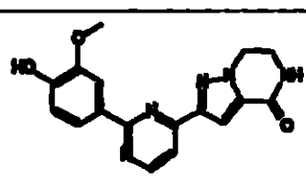
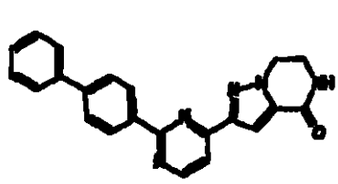
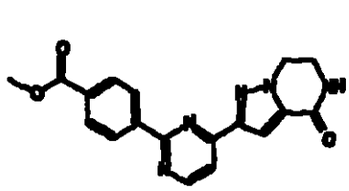
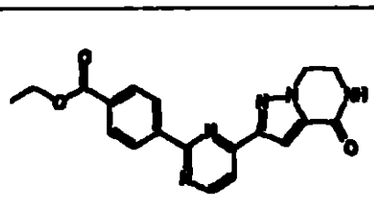
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203		2-[2-(3-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	
204		2-[2-(3-clorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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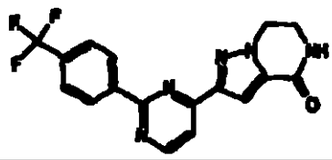
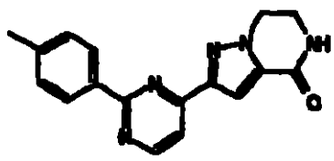
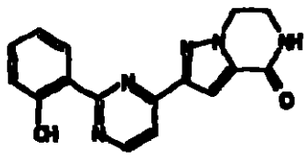
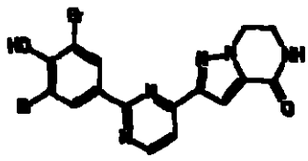
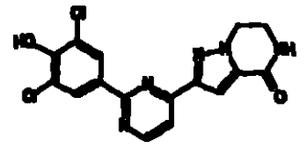
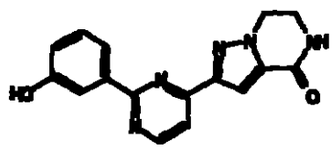
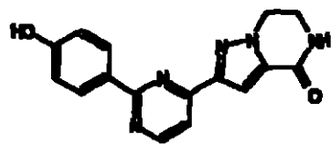
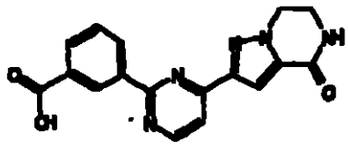
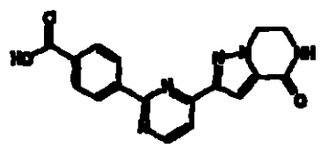
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213		2-[2-(3-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
214		2-[2-(4-bromofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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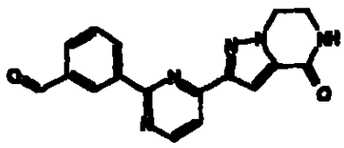
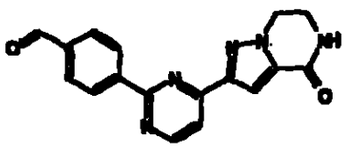
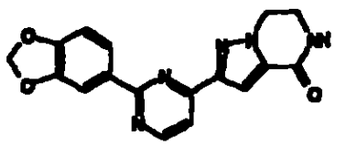
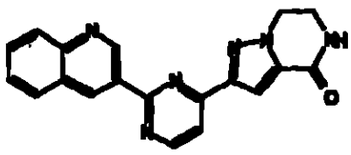
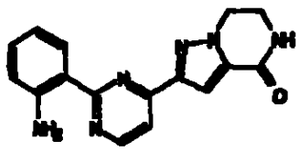
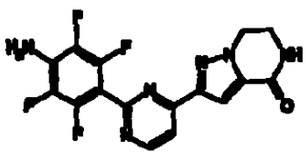
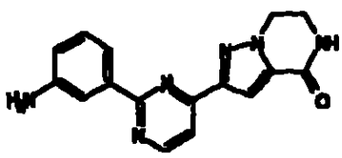
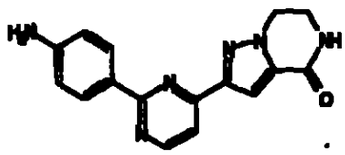
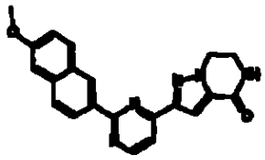
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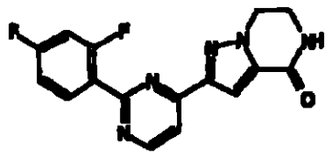
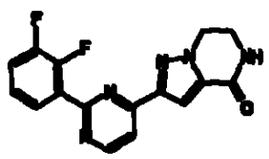
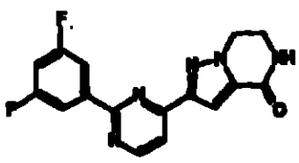
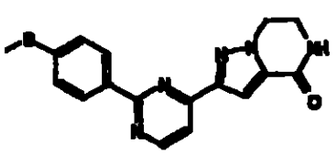
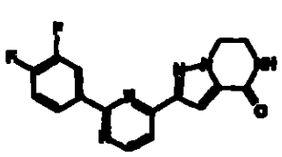
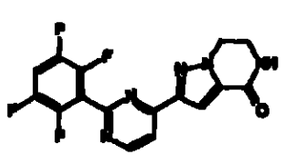
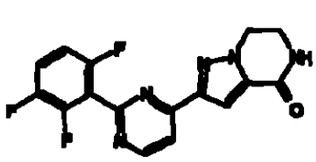
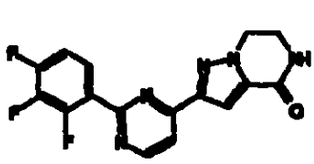
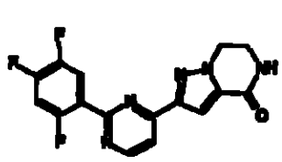
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218		2-{2-[4-(dimetilamino)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
219		2-[2-(4-metoxifenil)pirimidin-4-il)]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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221		2-[2-(4-hidroxi-3-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
222		2-[2-(1,1'-bifenil-4-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
223		metil 4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoato	
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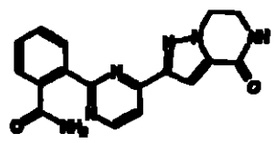
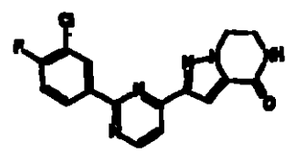
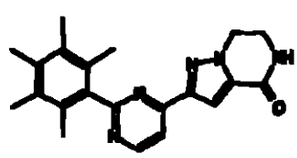
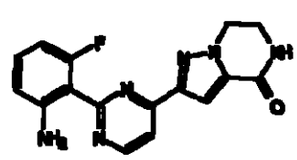
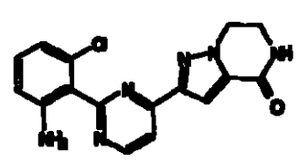
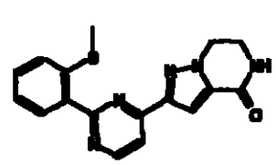
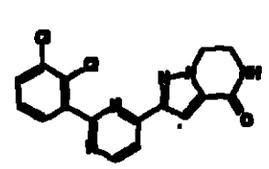
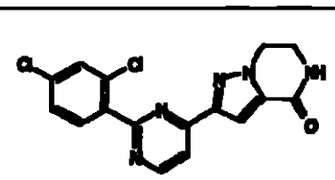
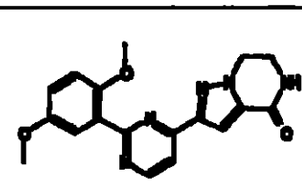
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226		2-[2-(4-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
227		2-[2-(2-hidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
228		2-[2-(3,5-dibromo-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
229		2-[2-(3,5-dicloro-4- hidroxifenil) pirimidin-4-il)]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
230		2-[2-(3-hidroxifenil)pirimidin-4-il]-6, 7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
231		2-[2-(4-hidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
232		ácido 3- [4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]benzoico	
233		ácido 4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]benzoico	

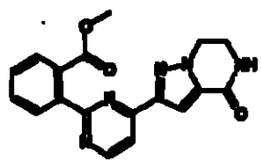
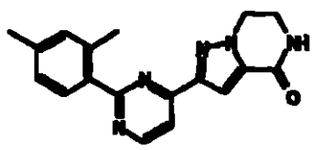
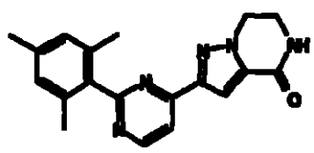
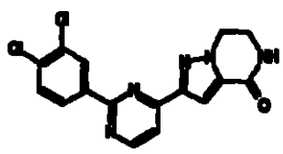
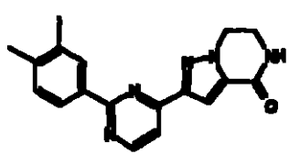
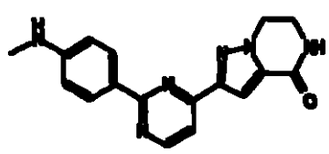
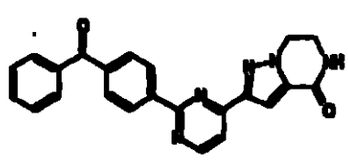
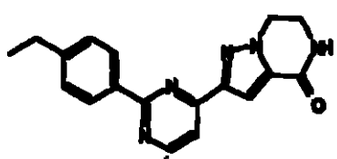
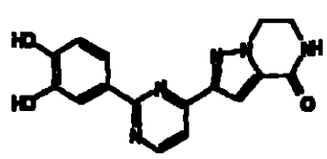
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234		3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] benzaldehído	
235		4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] benzaldehído	
236		2-[2-(1,3-benzodioxol-5-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
237		2-(2-quinolin-3-ilpirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
238		2-[2-(2-aminofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
239		2-[2-(4-amino-2,3,5,6-tetrafluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
240		2-[2-(3-aminofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
241		2-[2-(4-aminofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
242		2-[2-(6-metoxi-2-naftil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

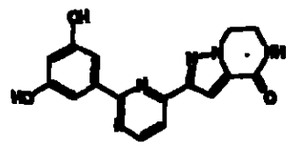
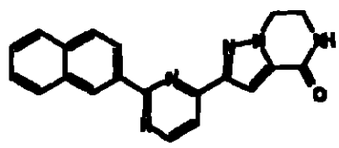
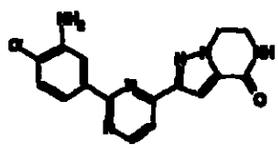
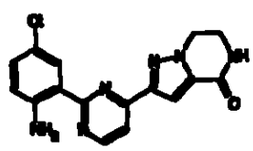
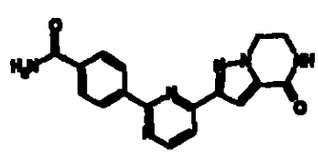
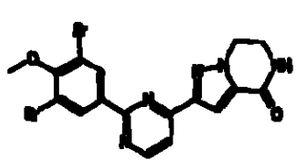
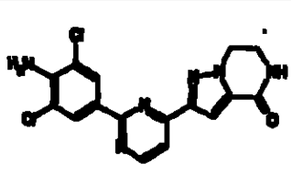
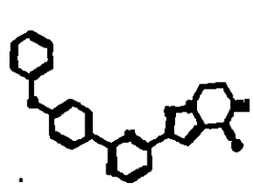
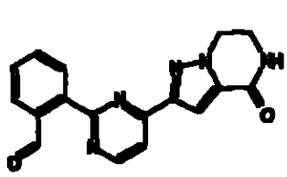
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244		2-[2-(2,3-difluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
245		2-[2-(3,5-difluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
246		2-[2-[4-(metiltio)fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
247		2-[2-(3,4-difluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
248		2-[2-(2,3,5,6-tetrafluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
249		2-[2-(2,3,6-trifluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
250		2-[2-(2,3,4-trifluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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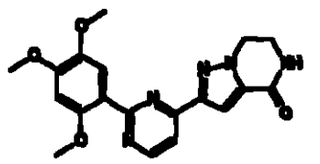
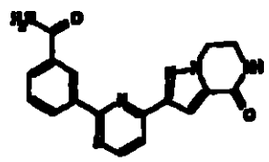
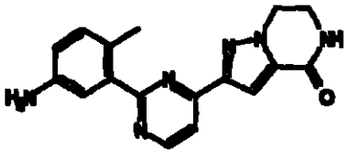
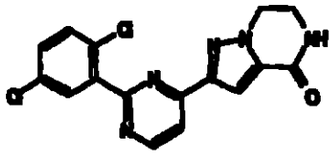
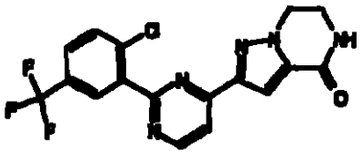
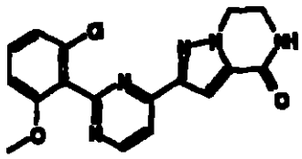
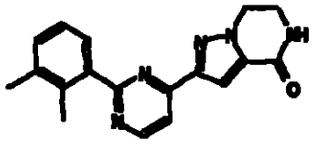
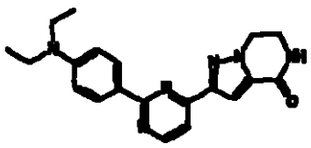
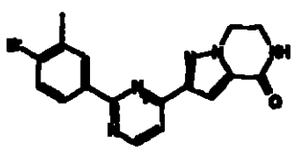
203-213

252		2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] benzamida	
253		2-[2-(3-cloro-4-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
254		2-[2-(pentametilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
255		2-[2-(2-amino-6-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
256		2-[2-(2-amino-6-clorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
257		2-[2-[2-(metiltio)fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
258		2-[2-(2,3-diclorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
259		2-[2-(2,4-diclorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
260		2-[2-(2,5-dimetoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

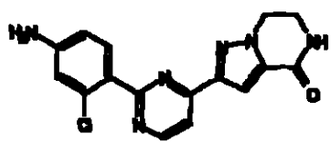
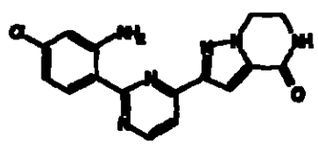
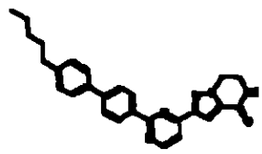
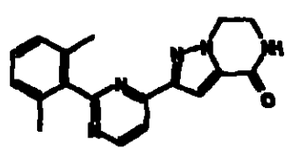
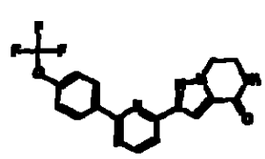
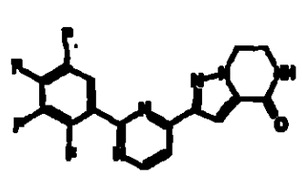
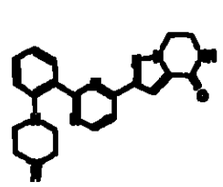
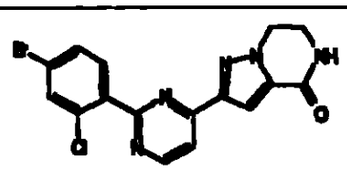
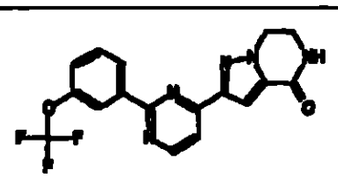
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262		2-[2-(2,4-dimetilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
263		2-(2-mesitilpirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
264		2-[2-(3,4-diclorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
265		2-[2-(3,4-dimetilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
266		2-(2-[4-(metilamino)fenil]pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
267		2-[2-(4-benzoilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
268		2-[2-(4-etilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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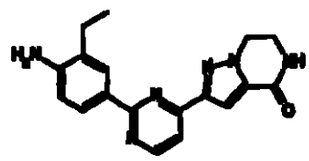
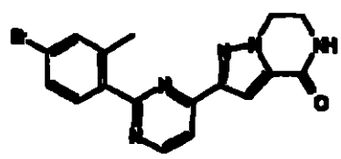
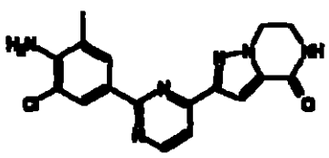
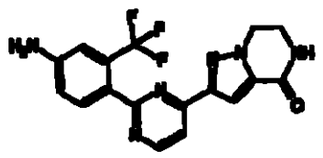
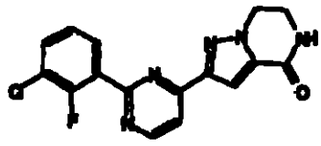
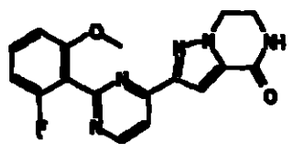
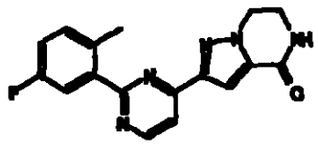
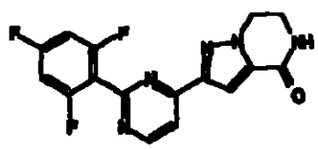
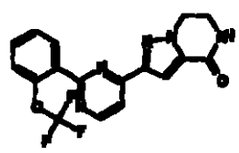
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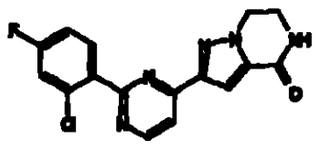
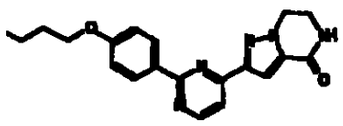
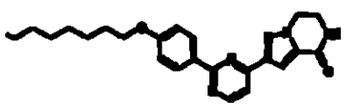
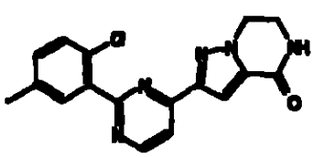
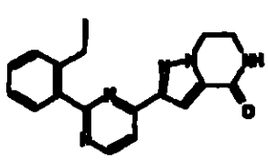
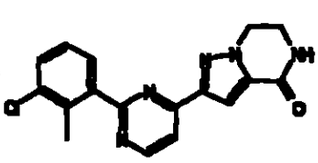
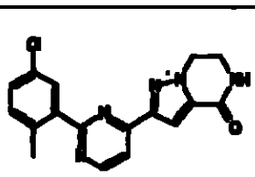
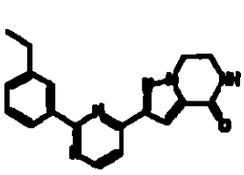
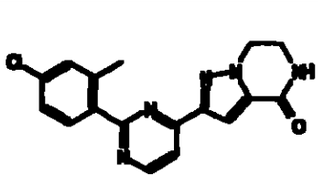
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273		2-[2-(2-amino-5-clorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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275		2-[2-(3,5-dibromo-4-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
27		2-[2-(4-amino-3,5-diclorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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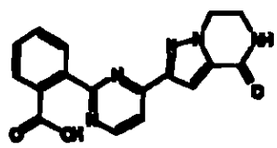
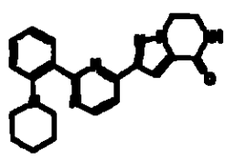
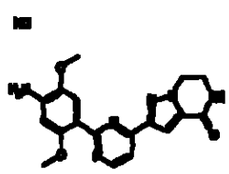
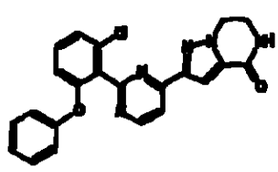
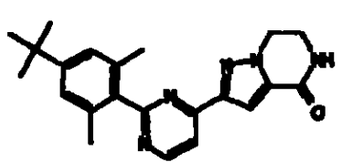
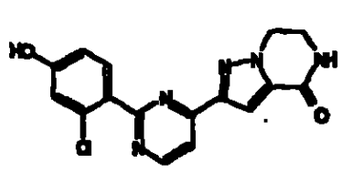
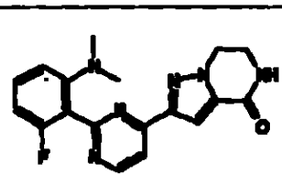
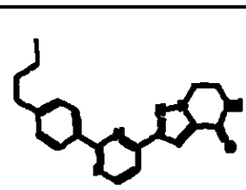
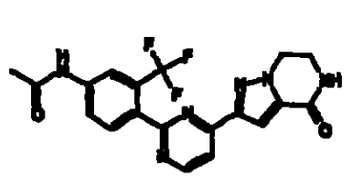
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284		2-[2-(2-cloro-6-metoxifenil) pirimidin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
285		2-[2-(2,3-dimetilfenil)pirimidin-4-il]-6,7 dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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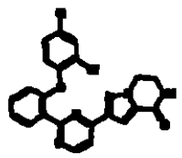
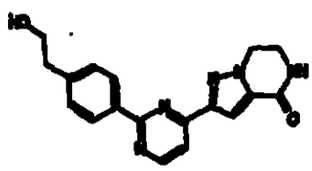
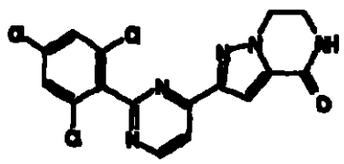
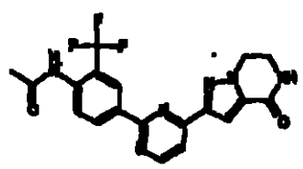
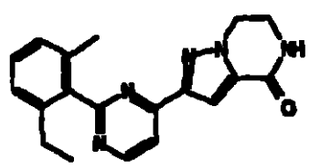
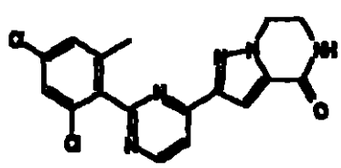
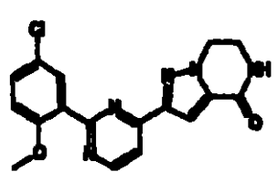
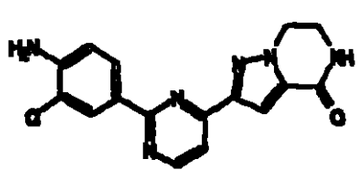
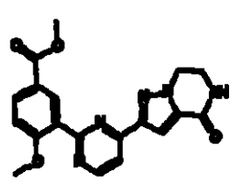
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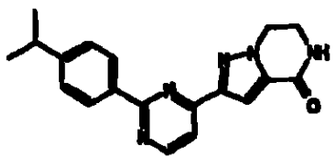
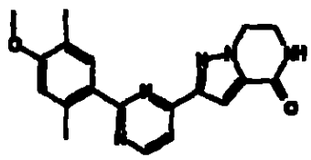
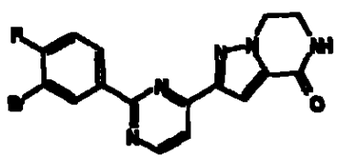
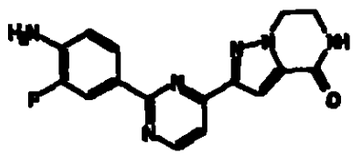
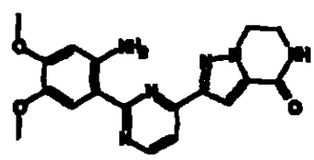
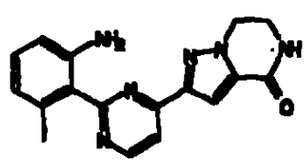
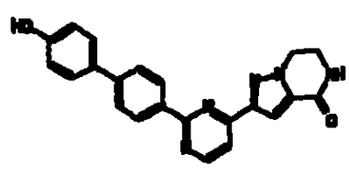
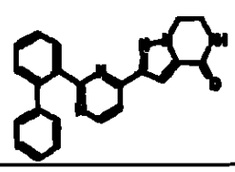
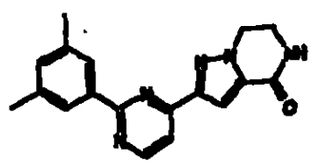
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293		2-[2-(2,3,4,5-tetrafluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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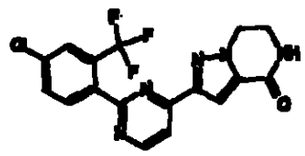
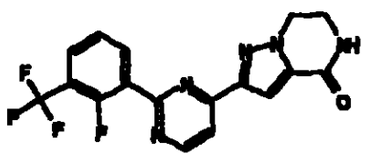
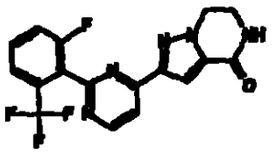
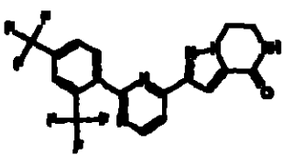
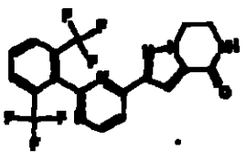
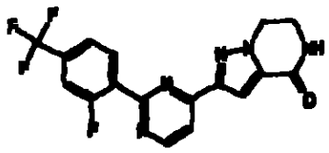
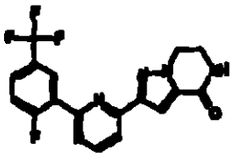
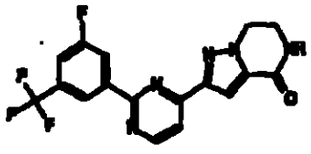
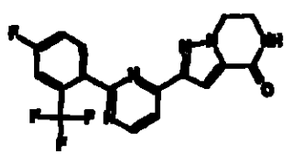
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298		2-[2-(4-bromo-2-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
299		2-[2-(4-amino-3-cloro-5-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
300		2-[2-[4-amino-2-(trifluorometil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
301		2-[2-(3-cloro-2-fluorofenil)pirimidin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
302		2-[2-(2-fluoro-6-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
303		2-[2-(5-fluoro-2-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
304		2-[2-(2,4,6-trifluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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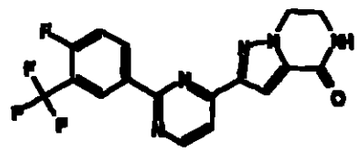
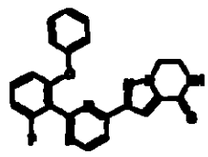
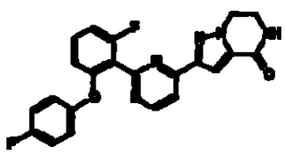
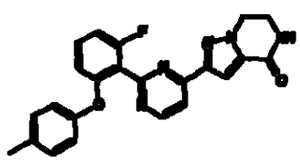
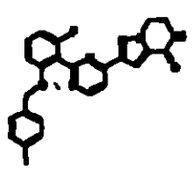
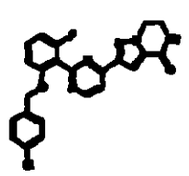
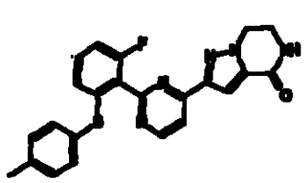
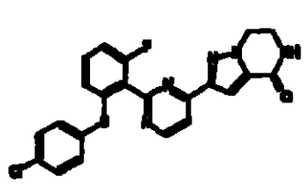
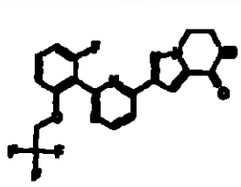
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307		2-[2-(4-butoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
308		2-[2-[4-(octiloxi)fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
309		2-[2-(2-cloro-5-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
310		2-[2-(2-etilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
311		2-[2-(3-cloro-2-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
312		2-[2-(5-cloro-2-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
313		2-[2-(3-etilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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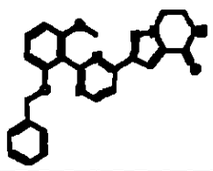
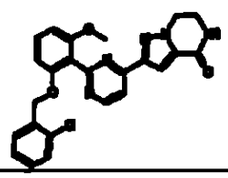
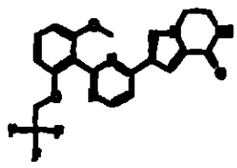
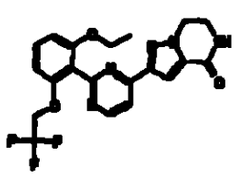
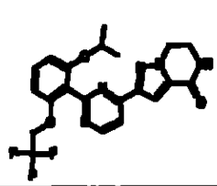
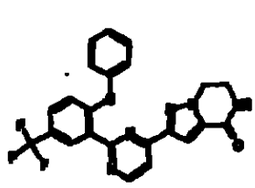
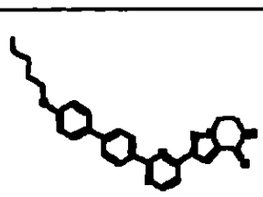
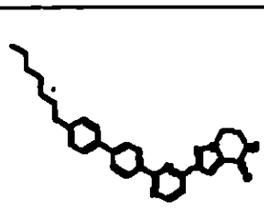
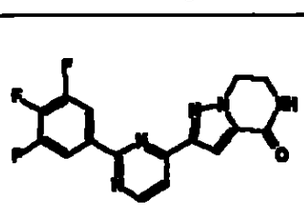
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316		2-[2-(2-piperidin-1-ilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
317		clorhidrato de 2-[2-(4-amino-2,5-dimetoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
318		2-[2-(2-cloro-6-fenoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
319		2-[2-(4-terc-butil-2,6- dimetilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
320		2-[2-(2-cloro-4-hidroxifenil) pirimidin-4- il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
321		2-(2-[2-(dimetilamino)-6-fluorofenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
322		2-[2-(4-butilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
323		N-[4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]-3-(trifluorometil) fenil]acetamida	

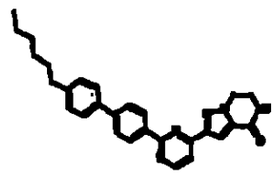
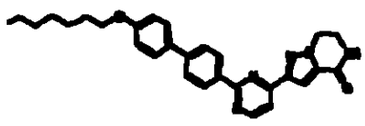
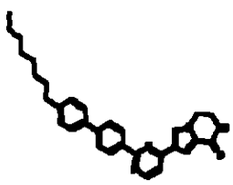
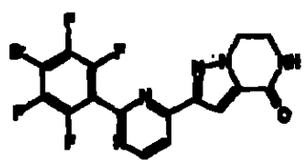
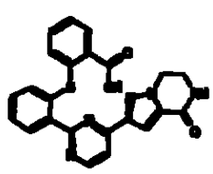
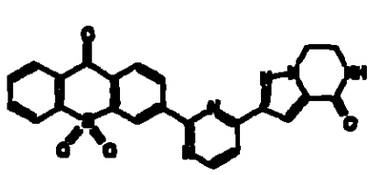
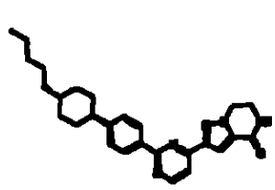
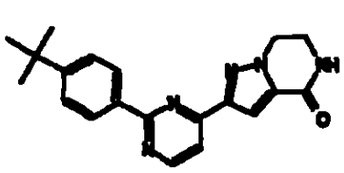
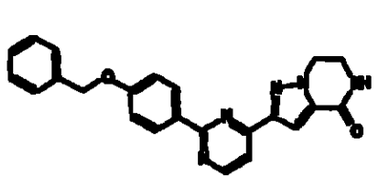
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325		2-[2-[4-(2-hidroxietil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
326		2-[2-(2,4,6-triclorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
327		N-[4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]-2-(trifluorometil) fenil]acetamida	
328		2-[2-(2-etil-6-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
329		2-[2-(2,4-dicloro-6-metilfenil) pirimidin-4-il)]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
330		2-[2-(5-cloro-2-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
331		2-[2-(4-amino-3-clorofenil)pirimidin-4-il)]-6,7-dihidropirazolol[1,5-a]pirazin-4(5H)-ona	
332		metil 4-metoxi-3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoato	

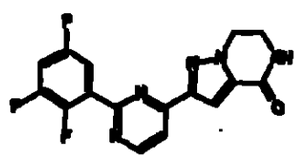
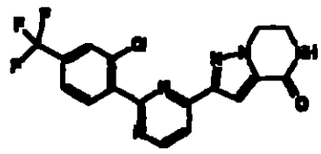
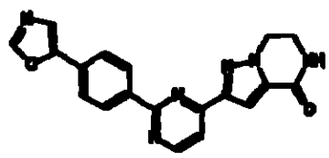
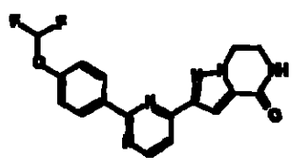
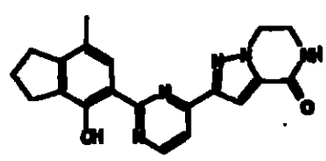
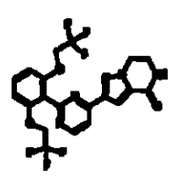
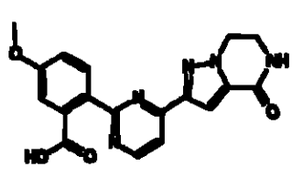
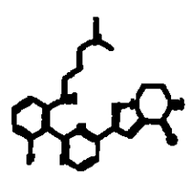
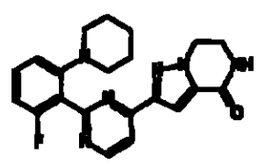
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334		2-[2-(4-metoxi-2,5-dimetilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
335		2-[2-(3-bromo-4-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
336		2-[2-(4-amino-3-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
337		2-[2-(2-amino-4,5-dimetoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
338		2-[2-(2-amino-6-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
339		2-[2-(4'-hidroxi-1,1'-bifenil-4-il)pirimidin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
340		2-[2-(1,1'-bifenil-2-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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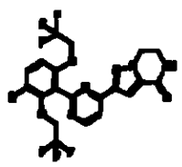
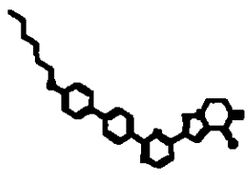
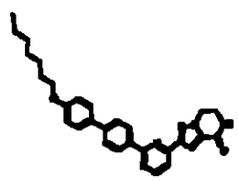
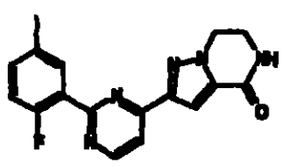
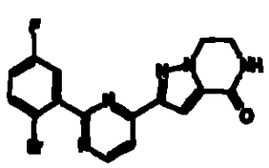
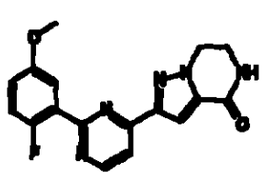
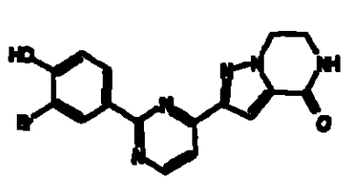
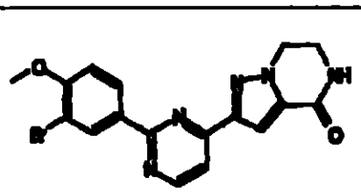
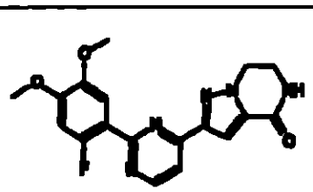
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343		2-{2-[2-fluoro-3-(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
344		2-{2-[2-fluoro-6-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
345		2-{2-[2, 4-bis(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
346		2-{2-[2, 6-bis(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
347		2-{2-[2-fluoro-4-(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
348		2-{2-[2-fluoro-5-(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
349		2-{2-[3-fluoro-5-(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
350		2-{2-[4-fluoro-2-(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

351		2-[2-[4-fluoro-3-(trifluorometil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
352		2-[2-(2-fluoro-6-fenoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
353		2-[2-[2-fluoro-6-(4-fluorofenoxi) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
354		2-[2-[2-fluoro-6-(4-metilfenoxi) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
355		2-(2-[2-fluoro-6-[(4-metilbencil)oxi] fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
356		2-(2-{2-[(4-clorobencil)oxi]-6-fluorofenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
357		2-(2-[2-fluoro-6-[(4-metilfenil)tio] fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
358		2-(2-{2-[(4-clorofenil)tio]-6-fluorofenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
359		2-[2-[2-fluoro-6-(2,2,2-trifluoroetoxi) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

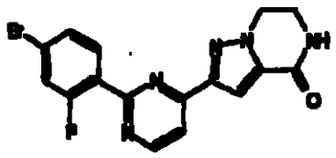
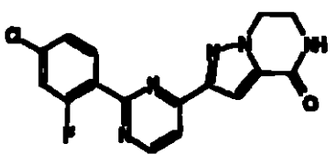
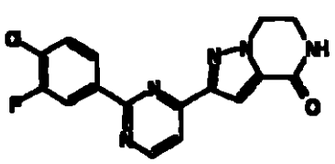
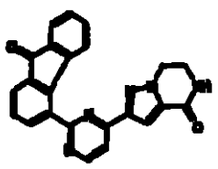
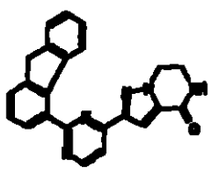
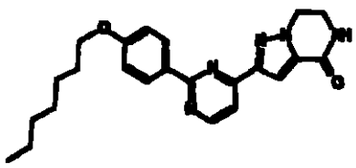
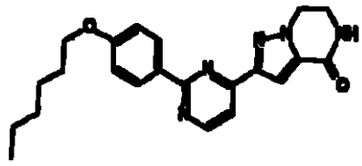
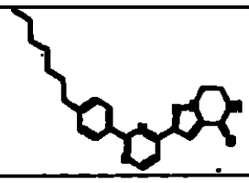
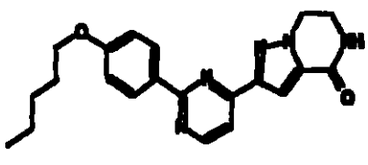
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362		2-{2-[2-metoxi-6-(2,2,2- trifluoroetoxi) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
363		2-{2-[2-etoxi-6-(2,2,2-trifluoroetoxi) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
364		2-{2-[2-isopropoxi-6-(2, 2, 2-trifluoroetoxi)fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
365		2-{2-[2-(feniltio)-5-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
366		2-{2-[4'-(pentiloxi)-1,1'-bifenil-4-il] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
367		2-[2-(4'-heptil-1,1'-bifenil-4-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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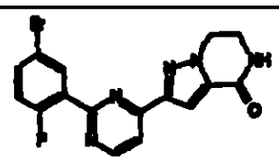
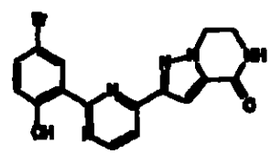
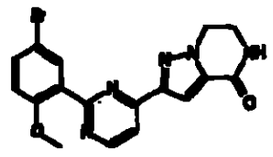
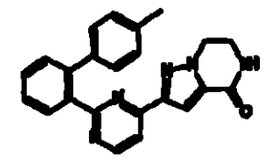
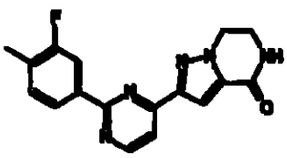
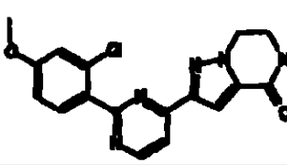
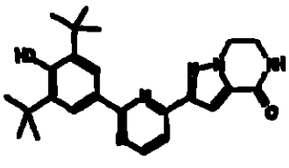
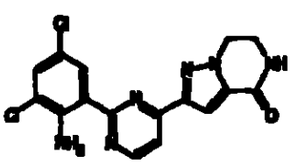
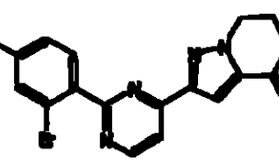
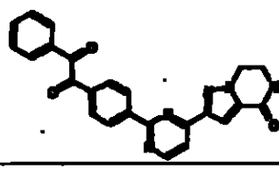
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370		2-[2-[4'-(octiloxi)-1,1'-bifenil-4-il] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
371		2-[2-(4-octil-1,1-bifenil-4-il)pirimidin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
372		2-[2-(4-bromo-2,3,5,6-tetrafluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
373		ácido 2-({2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil}tio)benzoico	
374		2-[2-(10,10-dioxido-9-oxo-9H-tioxanten-3-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
375		2-[2-[4-(4-pentilciclohexil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
376		2-[2-(4-terc-butilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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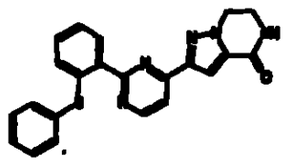
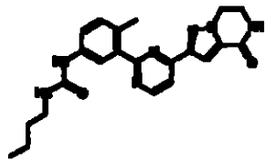
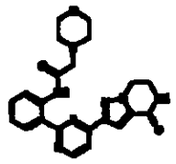
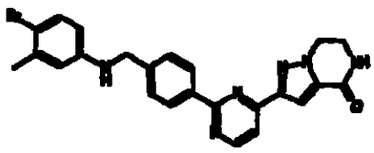
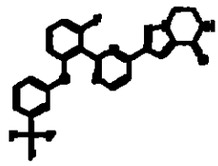
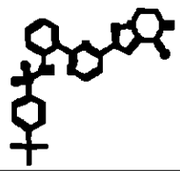
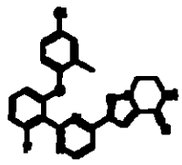
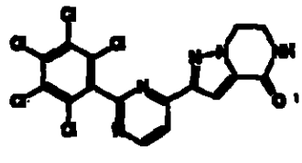
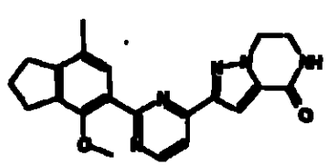
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379		2-[2-[2-cloro-4-(trifluorometil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
380		2-[2-[4-(1,3-oxazol-5-il)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
381		2-[2-[4-(difluorometoxi)fenil] pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
382		2-[2-(4-hidroxi-7-metil-2,3-dihidro-1H-inden-5-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
383		2-[2-[2,6-bis(2,2,2-trifluoroetoxi) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
384		ácido 5-metoxi-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoico	
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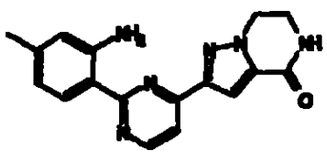
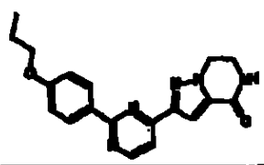
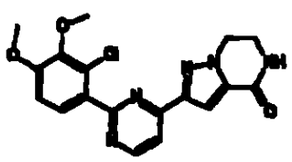
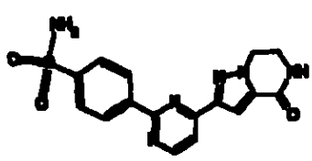
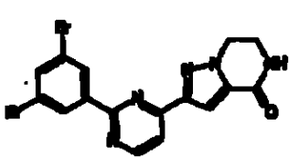
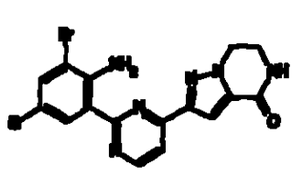
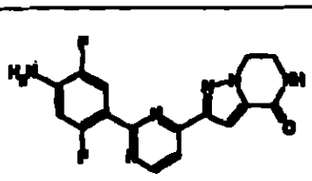
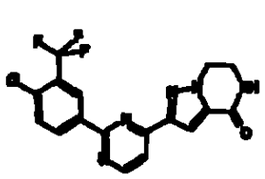
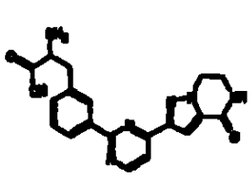
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388		2-[2-[4'-(hexiloxi)-1,1'-bifenil-4-il] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
389		2-[2-[4'-(heptiloxi)-1,1'-bifenil-4-il] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
390		2-[2-(2-fluoro-5-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
391		2-[2-(2-bromo-5-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
392		2-[2-(2-fluoro-5-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
393		2-[2-(3-bromo-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
394		2-[2-(3-bromo-4-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
395		2-[2-(2-fluoro-4,5-dimetoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

229

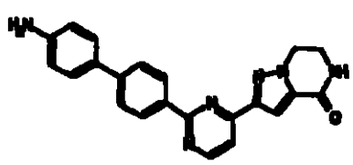
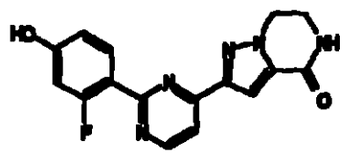
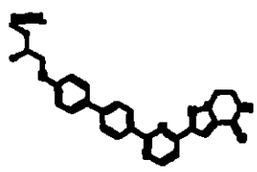
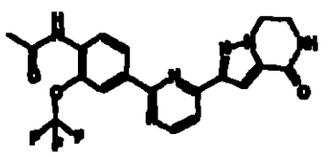
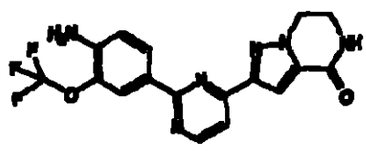
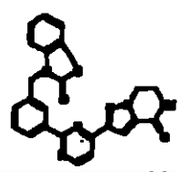
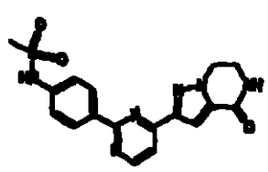
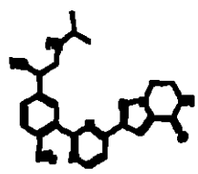
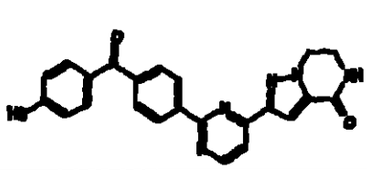
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397		2-[2-(4-cloro-2-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
398		2-[2-(4-cloro-3-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
399		2-[2-(9-oxo-9H-fluoren-4-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
400		2-[2-(9H-fluoren-4-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
401		2-{2-[4-(heptiloxi)fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
402		2-{2-[4-(hexiloxi)fenil]pirimidin-4-il}-6,7 dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
403		2-[2-(4-heptilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
404		2-{2-[4-(pentiloxi)fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

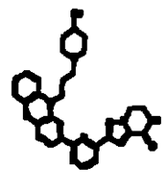
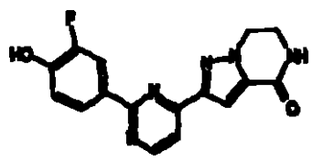
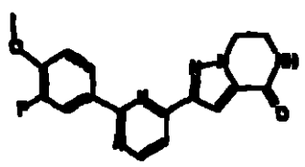
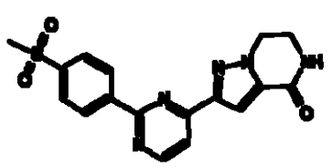
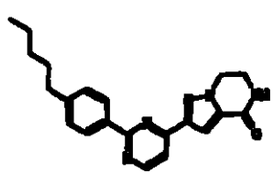
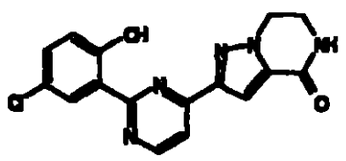
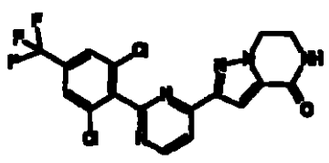
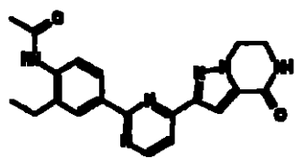
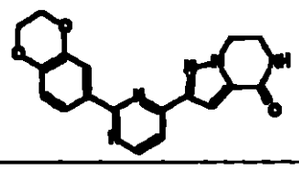
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406		2-[2-(5-bromo-2-hidroxifenil) pirimidin-4il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
407		2-[2-(5-bromo-2-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1, 5-a] pirazin-4 (5H)-ona	
408		2-[2-(4'-metil-1,1'-bifenil-2-il) pirimidin-4-il]-6,7-dihidropirazolo [1, 5-a] pirazin-4 (5H)-ona	
409		2-[2-(3-fluoro-4-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4 (5H)-ona	
410		2-[2-(2-cloro-4-metoxifenil) pirimidin-4il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
411		2-[2-(3,5-di-terc-butil-4- hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo [1,5-a] pirazin-4 (5H)-ona	
412		2-[2-(2-amino-3,5-diclorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	
413		[2-(2-bromo-4-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
414		1-(4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil}-2-feniletano-1,2-diona	

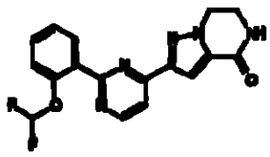
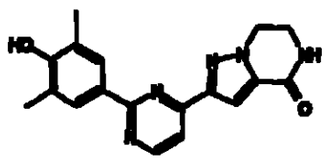
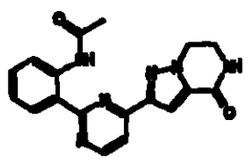
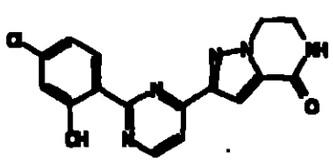
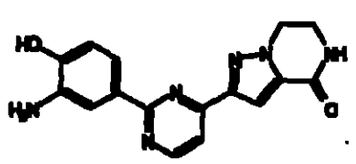
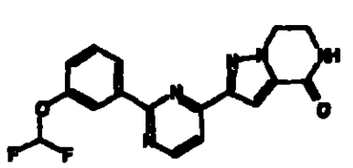
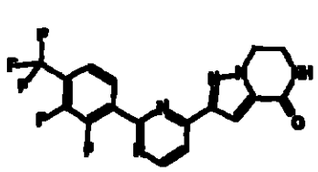
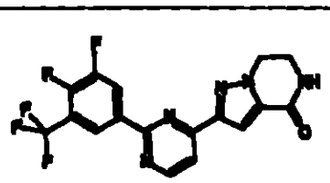
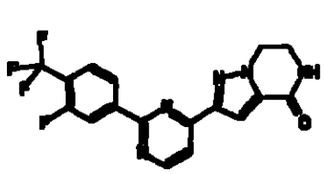
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416		N-butil-N'-{4-metil-3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenil}urea	
417		2-morfolin-4-il-N-{2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenil}acetamida	
418		2-[2-(4-{[(4-bromo-3-metilfenil)amino]metil}fenil)pirimidin-4-il]-6, 7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
419		2-(2-[2-fluoro-6-[3-(trifluorometil)fenoxi]fenil}pirimidin-4il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
420		4-terc-butil-N-{2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenil}bencenosulfonamida	
421		2-[2-[2-(4-cloro-2-metilfenoxi)-6-fluorofenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona	
422		2-[2-(pentaclorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
423		2-[2-(4-metoxi-7-metil-2,3-dihidro-1H-inden-5-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

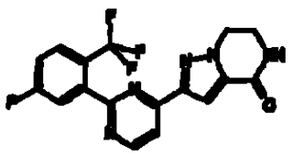
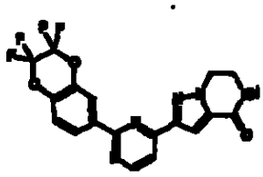
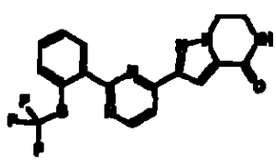
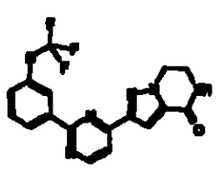
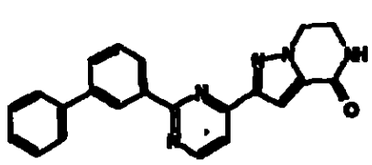
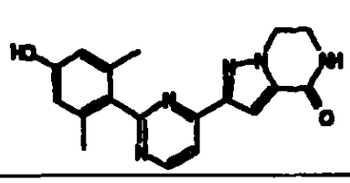
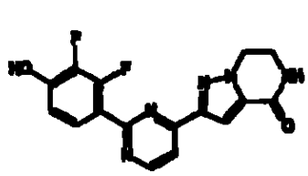
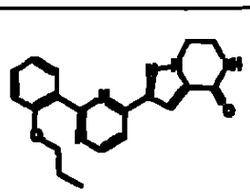
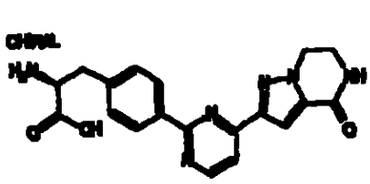
424		2-[2-(2-amino-4-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1, 5-a]pirazin-4(5H)-ona	
425		2-[2-(4-propoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
426		2-[2-(2-cloro-3,4-dimetoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
427		4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] bencenosulfonamida	
428		2-[2-(3,5-dibromofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4 (5H)-ona	
429		2-[2-(2-amino-3, 5-dibromofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
430		2-[2-(4-amino-2,5-difluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
431		2-{2-[4-cloro-3-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
432		3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] fenilalanina	

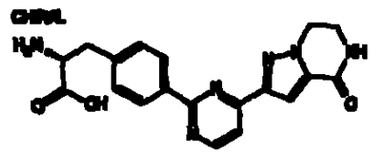
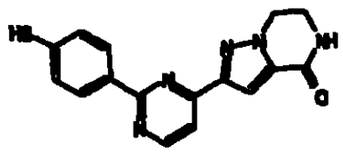
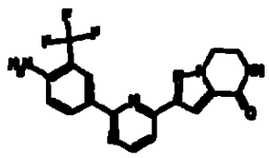
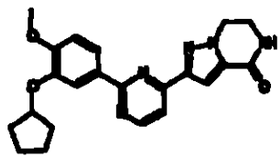
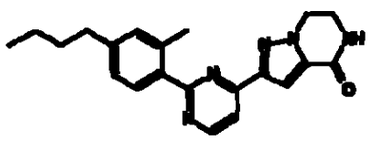
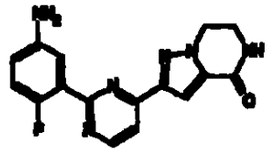
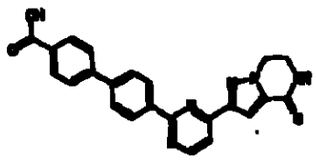
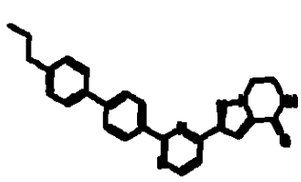
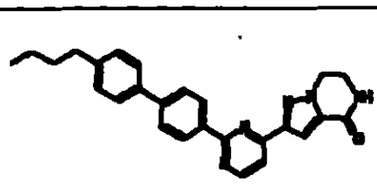
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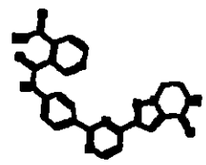
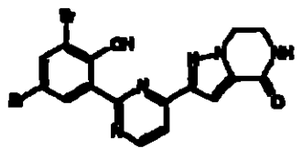
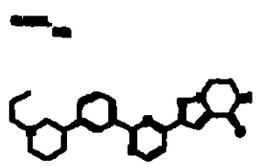
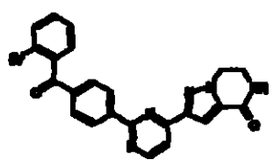
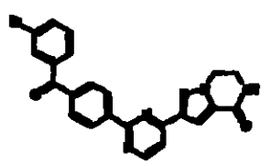
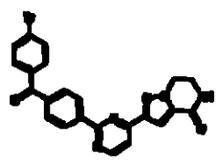
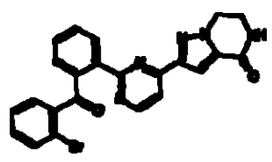
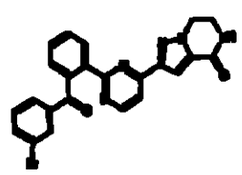
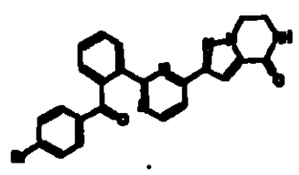
433		2-[2-(4'-amino-1,1'-bifenil-4-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
434		2-[2-(2-fluoro-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
435		2-[2-(4'-[[(2S)-2-metilbutil]oxi}-1,1'-bifenil-4-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
436		N-[4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-2-(trifluorometoxi) fenil]acetamida	
437		2-[2-[4-amino-3-(trifluorometoxi) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
438		2-(2-{3-[(2-oxo-1,3-benzoxazol-3(2H)- il)metil]fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
439		N-{4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenil} metanosulfonamida	
440		2-(2-{2-amino-5-[1-hidroxi-2-(isopropilamino)etil]fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
441		2-[2-[4-(4-mercaptobenzoil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

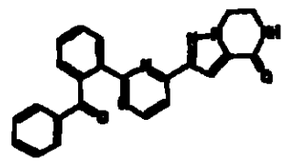
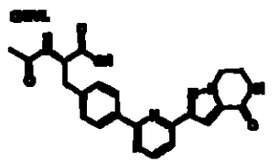
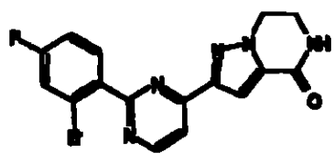
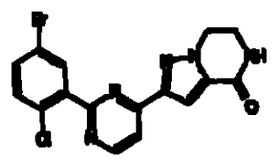
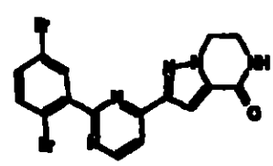
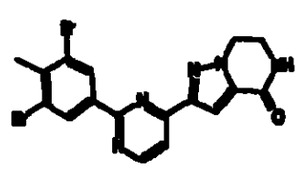
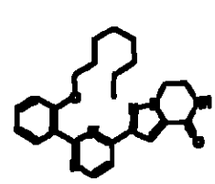
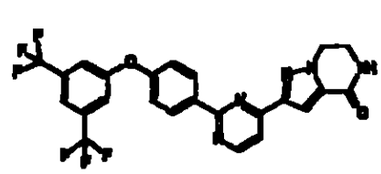
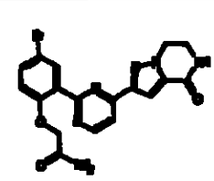
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443		2-[2-(3-fluoro-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
444		2-[2-(3-fluoro-4-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
445		2-[2-[4-(metilsulfonil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
446		2-[2-(4-pentilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
447		2-[2-(5-cloro-2-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
448		2-{2-[2,6-dicloro-4-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
449		N-{2-etil-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil}acetamida	
450		2-[2-(2,3-dihidro-1,4-benzodioxin-6-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

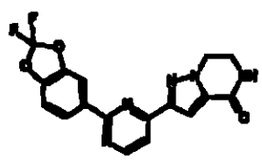
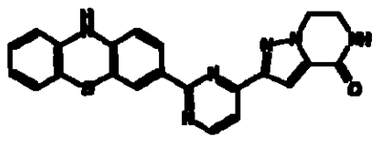
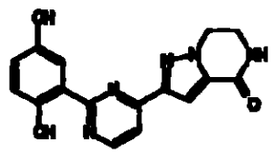
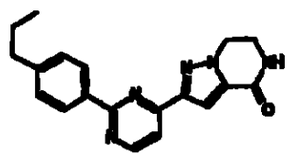
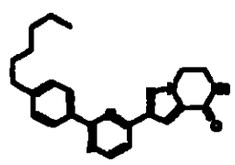
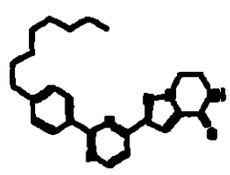
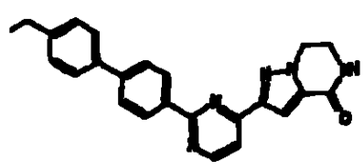
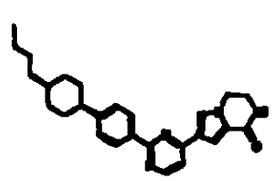
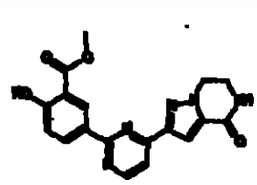
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452		2-[2-(4-hidroxi-3,5-dimetilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
453		N-[2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil]acetamida	
454		2-[2-(4-cloro-2-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
455		2-[2-(3-amino-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
456		2-[2-[3-(difluorometoxi)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
457		2-[2-[2,3-difluoro-4-(trifluorometil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
458		2-[2-[3,4-difluoro-5-(trifluorometil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
459		2-[2-[3-fluoro-4-(trifluorometil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

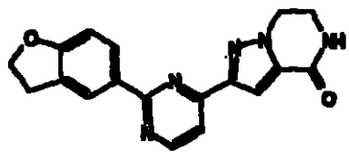
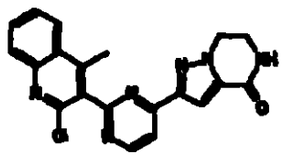
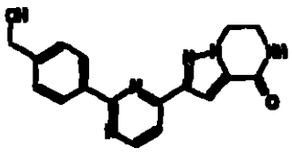
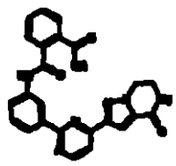
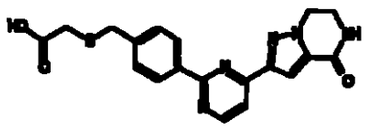
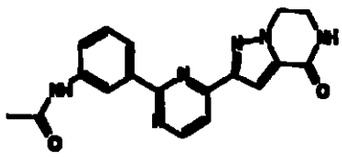
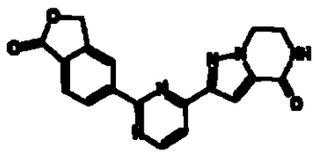
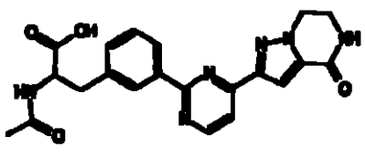
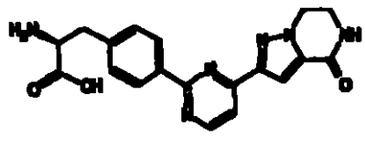
460		2-{2-[5-fluoro-2-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
461		2-[2-(2,2,3,3-tetrafluoro-2,3-dihidro-1,4- benzodioxin-6-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
462		2-(2-{2-[(trifluorometil)tio]fenil} pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
463		[(trifluorometil)tio]fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
464		2-[2-(1,1'-bifenil-3-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
465		2-[2-(4-hidroxi-2,6-dimetilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
466		2-[2-(2,3-difluoro-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
467		2-[2-(2-propoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
468		4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]-L-fenilalanina	

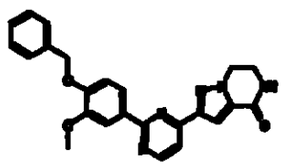
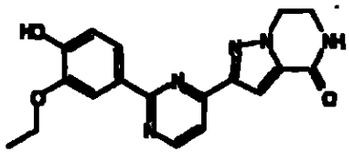
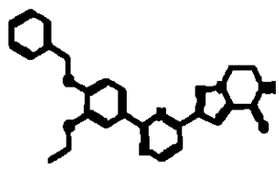
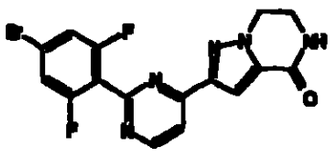
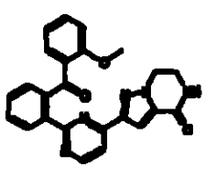
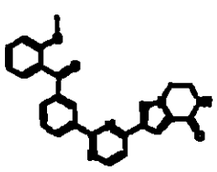
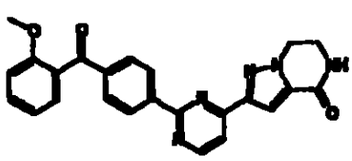
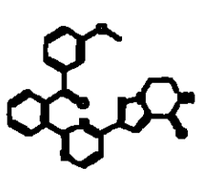
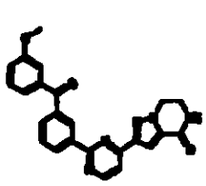
469		4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]-D-fenilalanina	
470		2-[2-(4-mercaptofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
471		2-[2-[4-amino-3-(trifluorometil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
472		2-[2-[3-(ciclopentiloxi)-4-metoxifenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
473		2-[2-(4-butil-2-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
474		2-[2-(5-amino-2-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
475		ácido 4'-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]-1,1'-bifenil-4-carboxílico	
476		2-[2-(4'-propil-1,1'-bifenil-4-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
477		2-[2-(4'-butil-1,1'-bifenil-4-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

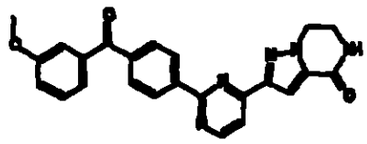
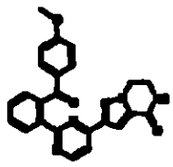
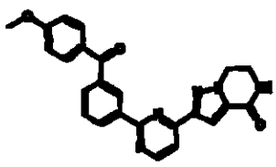
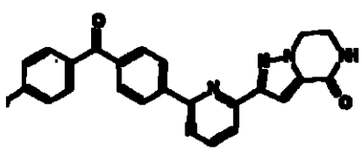
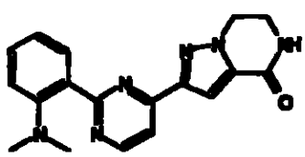
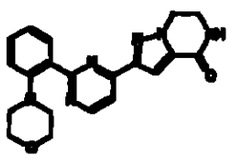
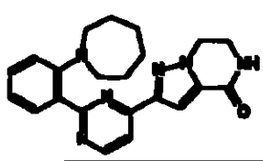
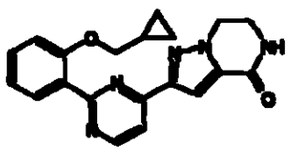
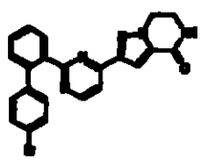
478		ácido 2-[({4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil)amino)carbonil] benzoico	
479		2-[2-(3,5-dibromo-2-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
480		clorhidrato de 2-(2-[3-[(3S)-1-propilpiperidin-3-il] fenil]pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
481		2-(2-(4-(2-bromobenzoil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
482		2-[2-[4-(3-bromobenzoil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
483		2-[2-[4-(4-bromobenzoil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
484		2-[2-[2-(2-bromobenzoil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
485		2-[2-[2-(3-bromobenzoil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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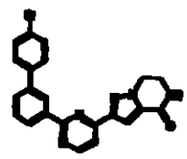
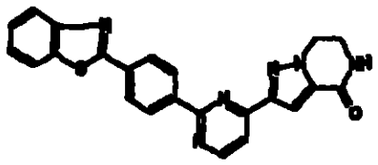
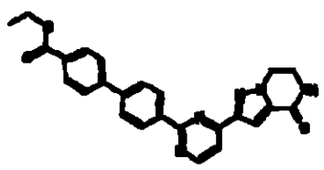
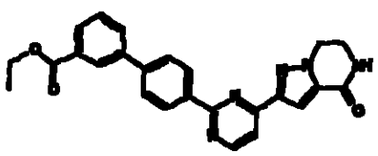
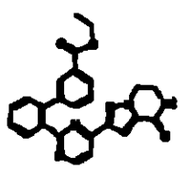
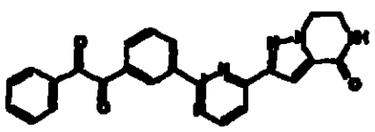
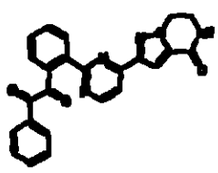
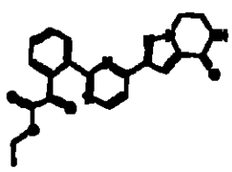
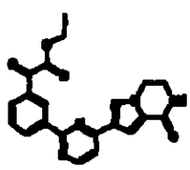
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488		N-acetil-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-L-fenilalanina	
489		2-[2-(2-bromo-4-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
490		2-[2-(5-bromo-2-clorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
491		2-[2-(2,5-dibromofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
492		2-[2-(3,5-dibromo-4-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
493		2-{2-[2-(octiloxi)fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
494		2-(2-{4-[3,5-bis(trifluorometil) fenoxi]fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
495		2-{4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il)]fenoxi}acetamida	

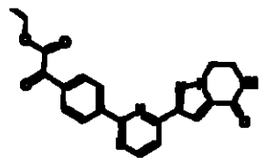
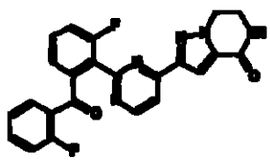
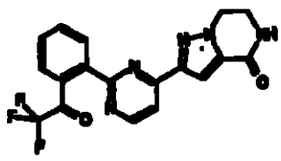
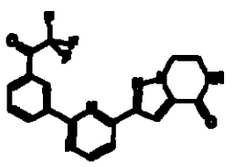
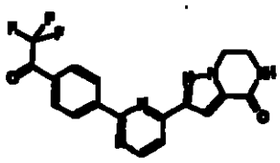
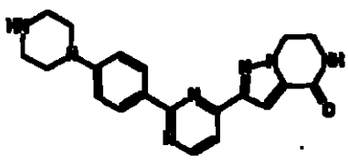
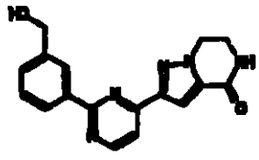
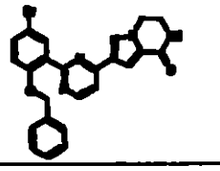
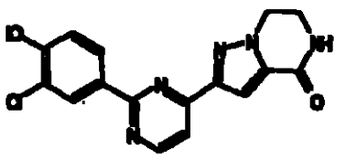
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497		2-[2-(10H-fenotiazin-3-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
498		2-[2-(2,5-dihidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
499		2-[2-(4-propilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
500		2-[2-(4-hexilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
501		2-[2-(4-octilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
502		2-[2-(4'-etil-1,1'-bifenil-4-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
503		2-[2-[4-(4-butilciclohexil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
504		metil 2-hidroxi-5-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]benzoato	

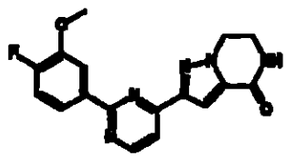
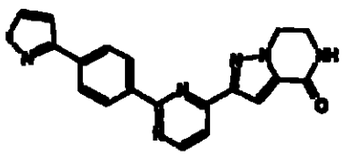
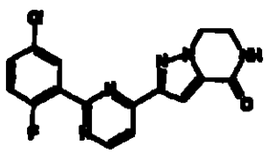
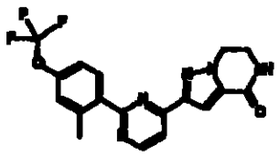
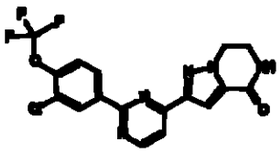
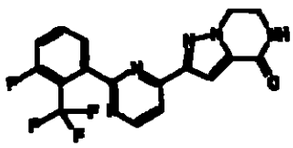
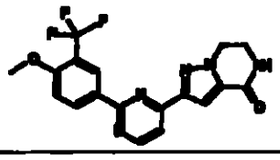
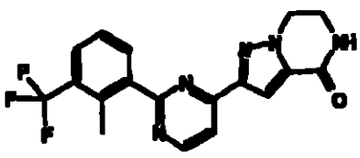
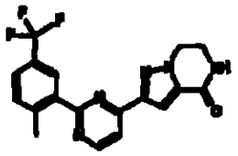
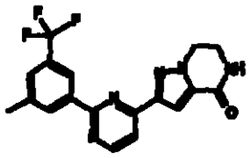
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506		2-[2-(2-cloro-4-metilquinolin-3-il)pirimidin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
507		2-[2-[4-(hidroximetil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
508		ácido 2-[({3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil}amino)carbonil] benzoico	
509		ácido ({4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il] bencil}tio)acético	
510		N-{3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil}acetamida	
511		2-[2-(1-oxo-1,3-dihidro-2-benzofuran-5- il)pirimidin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
512		N-acetil-3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il] fenilalanina	
513		4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]-L-fenilalanina	

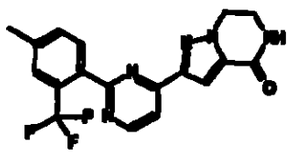
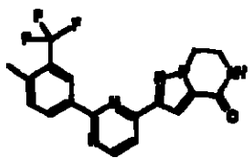
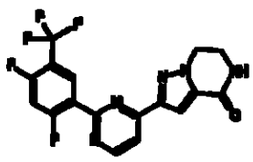
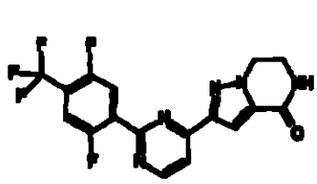
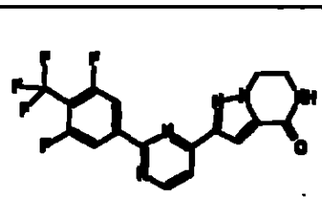
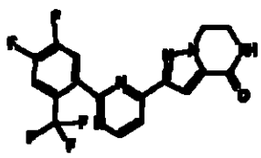
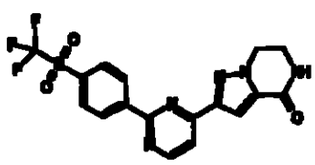
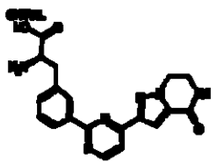
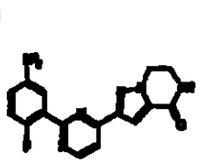
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515		2-[2-(3-etoxi-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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517		2-[2-(4-bromo-2,6-difluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
518		2-{2-[2-(2- metoxibenzoil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
519		2-{2-[3-(2-metoxibenzoil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
520		2-{2-[4-(2- metoxibenzoil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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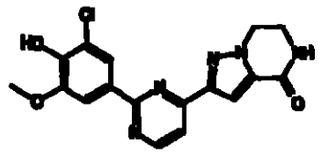
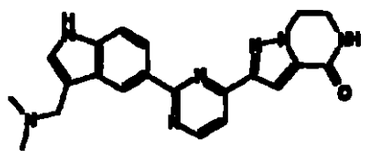
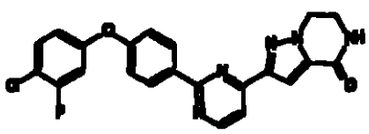
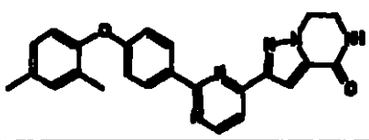
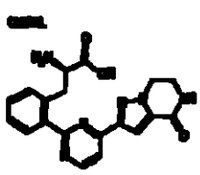
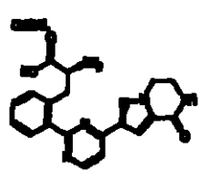
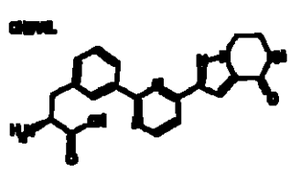
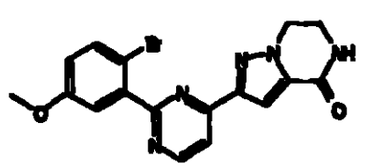
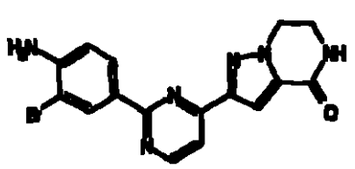
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530		2-{2-[2-(ciclopropilmetoxi)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
531		2-[2-(4'-bromo-1,1'-bifenil-2-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

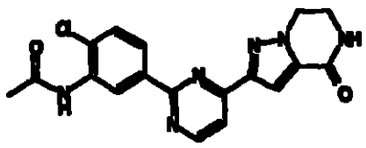
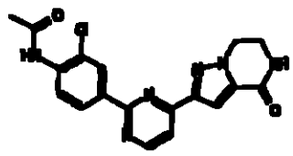
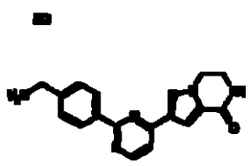
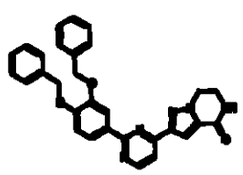
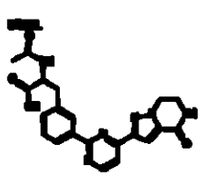
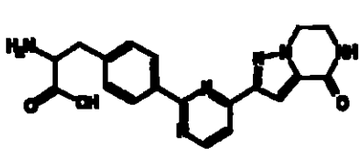
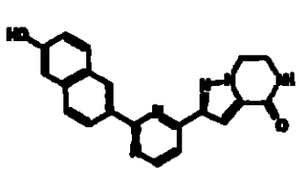
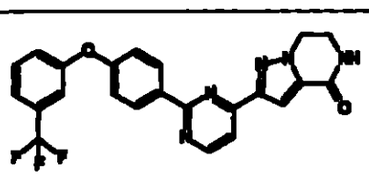
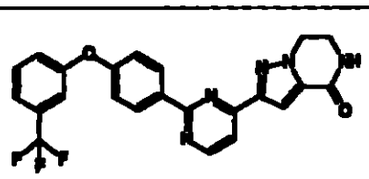
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533		2-{2-[4-(1,3-benzotiazol-2-il)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
534		etil 4'-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-1,1'-bifenil-4-carboxilato	
535		etil 4'-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-1,1'-bifenil-3-carboxilato	
536		etil 2'-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-1,1'-bifenil-3-carboxilato	
537		1-{3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]fenil}-2-feniletano-1,2-diona	
538		1-{2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il) pirimidin-2-il]fenil}-2-feniletano- 1,2-diona	
539		etil oxo[2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil]acetato	
540		etil oxo{3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil}acetato	

541		etil oxo[4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil]acetato	
542		2-[2-[2-fluoro-6-(2-fluorobenzoil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
543		2-[2-[2-(trifluoroacetil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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546		2-[2-(4-piperazin-1-ilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
547		2-[2-[3-(hidroximetil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
548		2-[2-[2-(benciloxi)-5- bromofenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
549		2-[2-(3-cloro-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

550		2-[2-(4-fluoro-3-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
551		2-{2-[4-(1 H-pirazol-3-il)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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559		2-{2-[3-metil-5-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

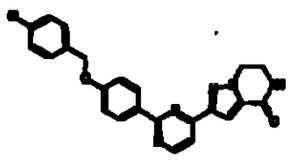
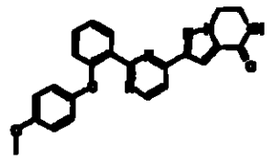
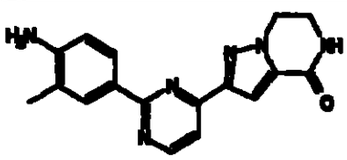
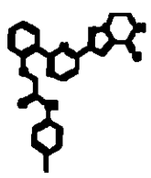
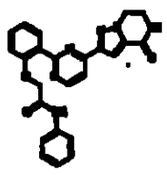
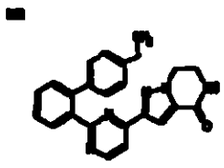
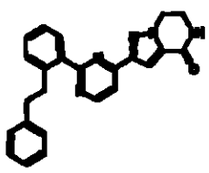
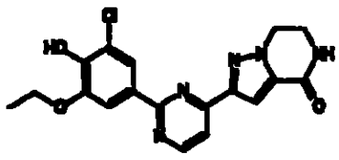
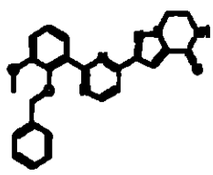
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561		2-{2-[4-metil-3-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
562		2-{2-[2, 4-difluoro-5-(trifluorometil) fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
563		2-{2-[2,5-difluoro-4-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
564		2-{2-[3,5-difluoro-4-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
565		2-{2-[4,5-difluoro-2-(trifluorometil) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
566		2-(2-[4-[(trifluorometil)sulfonil] fenil}pirimidin-4 il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
567		3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]-D-fenilalanina	
568		clorhidrato de 2-[2-(5-amino-2-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

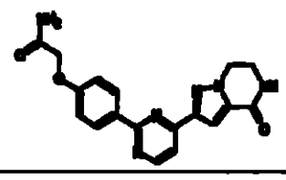
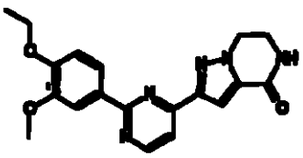
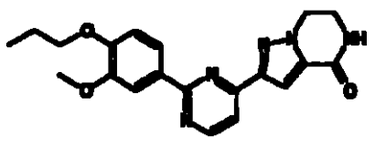
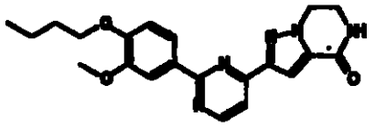
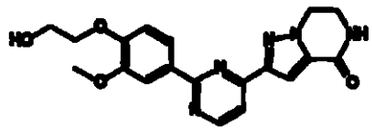
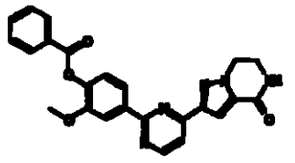
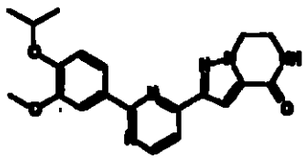
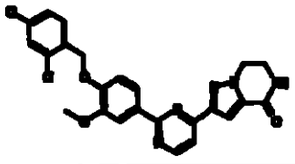
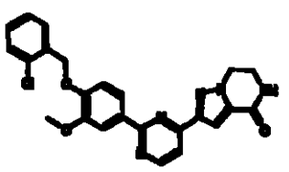
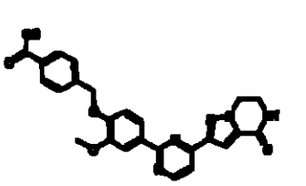
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570		2-(2-3-[(dimetilamino)metil]-1H-indol-5-il}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
571		2-[2-[4-(4-cloro-3-fluorofenoxi) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
572		2-[2-[4-(2,4-dimetilfenoxi)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
573		2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]-D-fenilalanina	
574		2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]-L-fenilalanina	
575		3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-L- fenilalanina	
576		2-[2-(2-bromo-5-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
577		2-[2-(4-amino-3-bromofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

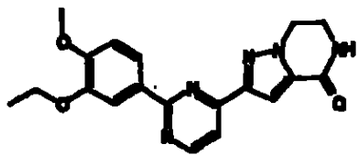
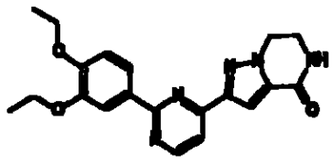
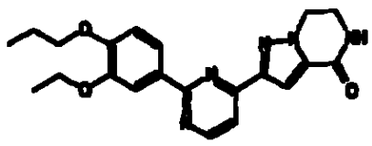
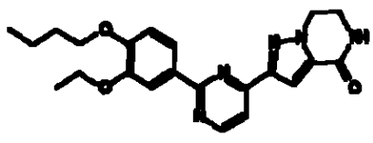
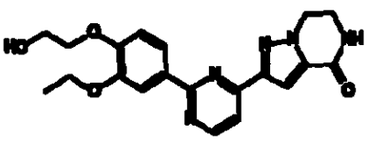
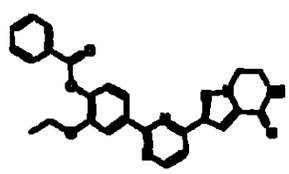
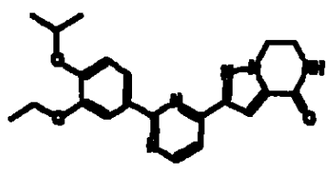
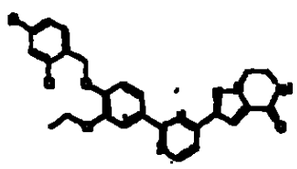
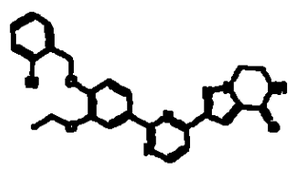
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579		N-[2-cloro-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil]acetamida	
580		2-[2-[4-(aminometil)fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona clorhidrato	
581		2-[2-[3,4-bis(benciloxi)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
582		N-acetil-3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-L-fenilalanina	
583		4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] fenilalanina	
584		2-[2-(6-hidroxi-2-naftil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
585		2-(2-[4-[3-(trifluorometil)fenoxi] fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
586		2-(2-[4-[(4-clorobencil)oxi]fenil} pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

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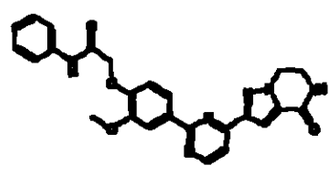
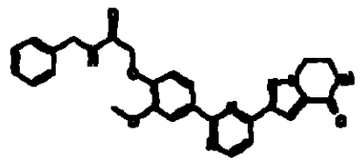
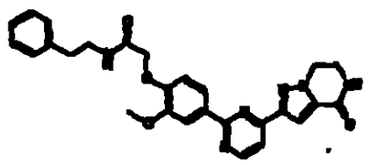
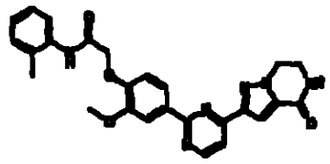
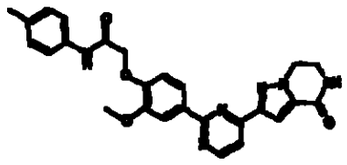
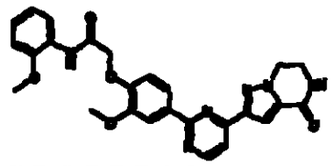
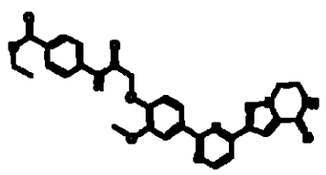
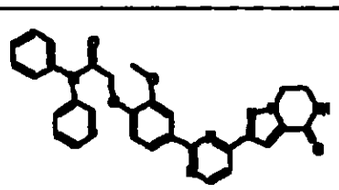
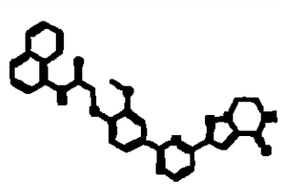
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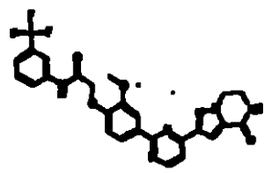
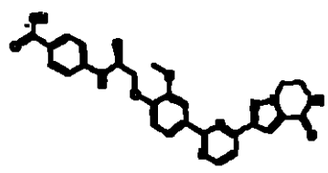
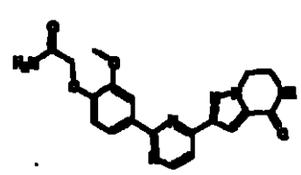
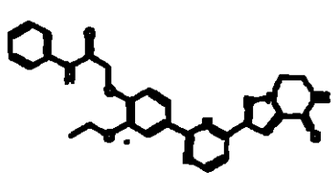
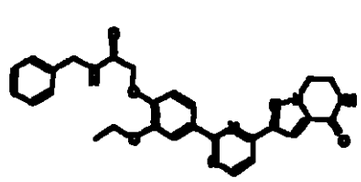
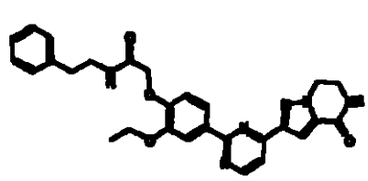
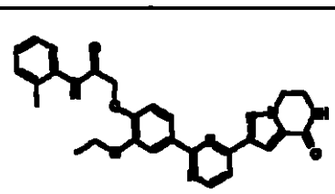
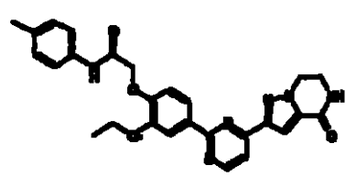
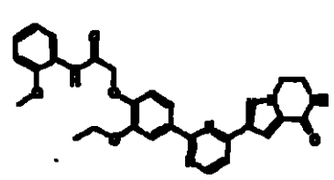
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588		clorhidrato de 2-[2-(4-piperazin-1-ilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
589		2-[2-(4-amino-3-metil fenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
590		N-(4-metilfenil)-2-{2-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi} acetamida	
591		2-{2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}-N-fenilacetamida	
592		clorhidrato de 2-{2-[4'-(aminometil)-1,1'-bifenil-2- il]pirimidin-4-il}-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
593		2-{2-[2-(2-feniletil)fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
594		2-[2-(3-cloro-5-etoxi-4-hidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
595		2-[2-[2-(benciloxi)-3-metoxifenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

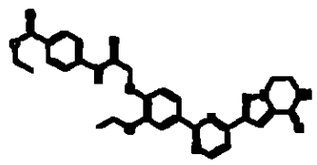
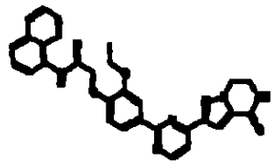
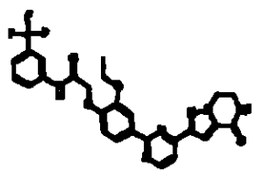
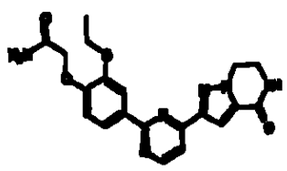
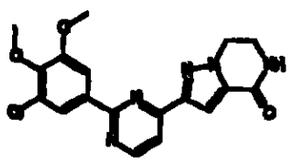
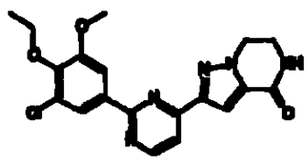
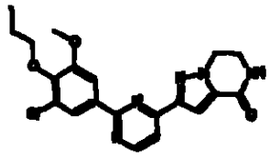
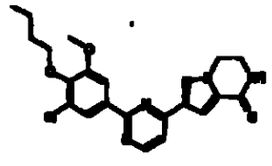
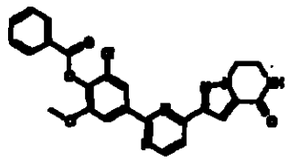
596		2-{4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}acetamida	
597		2-[2-(4-etoxi-3-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
598		2-[2-(3-metoxi-4-propoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
599		2-[2-(4-butoxi-3-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
600		2-[2-[4-(2-hidroxietoxi)-3-metoxifenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
601		2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenilbenzoato	
602		2-[2-(4-isopropoxi-3-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
603		2-{2-[4-[(2,4-diclorobencil)oxi]-3-metoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
604		2-{2-[4-[(2-clorobencil)oxi]-3-metoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
605		ácido 4-({2-metoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}metil)benzoico	

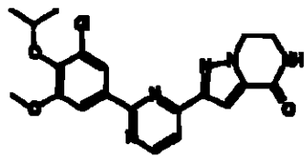
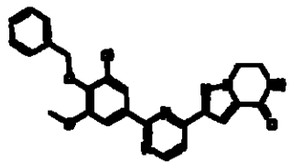
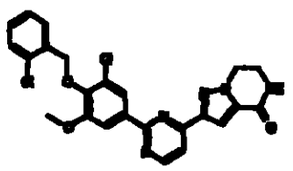
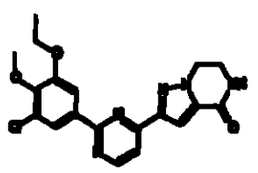
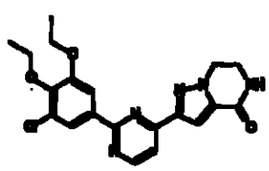
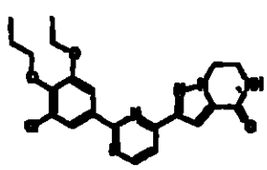
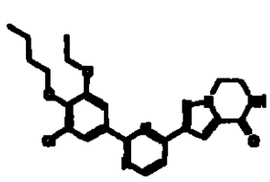
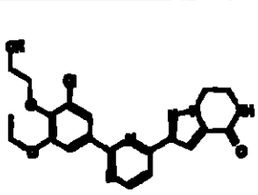
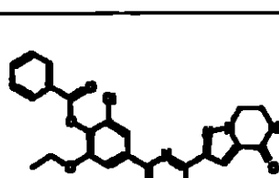
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607		2-[2-(3,4-dietoxifenil)pirimidin-4-il]-6,7 dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
608		2-[2-(3-etoxi-4-propoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
609		2-[2-(4-butoxi-3-etoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
610		2-{2-[3-etoxi-4-(2-hidroxietoxi) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
611		2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenilbenzoato	
612		2-[2-(3-etoxi-4-isopropoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
613		2-{2-[4-[(2,4-diclorobencil)oxi]-3-etoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a)pirazin-4(5H)-ona	
614		2-(2-{4-[(2-clorobencil)oxi]-3-etoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

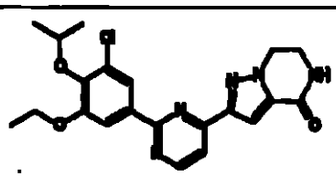
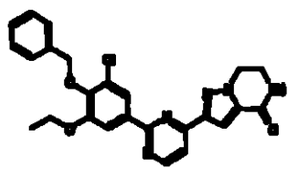
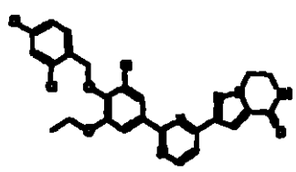
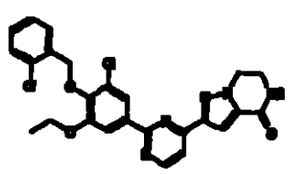
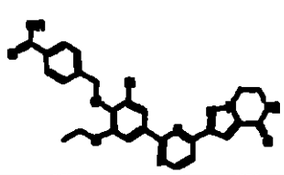
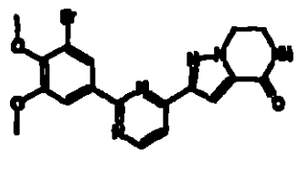
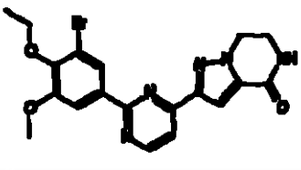
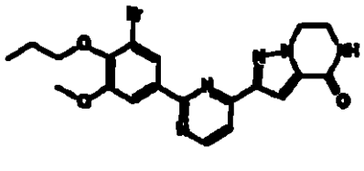
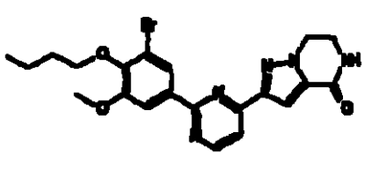
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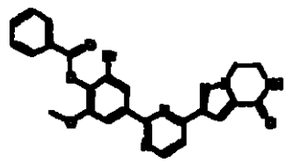
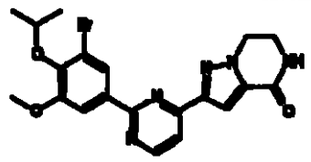
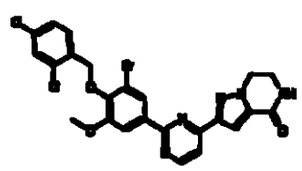
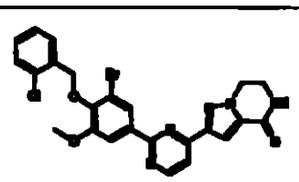
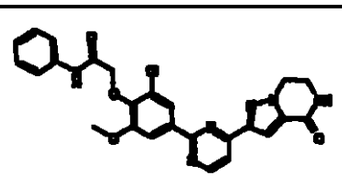
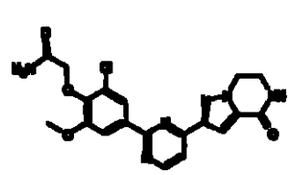
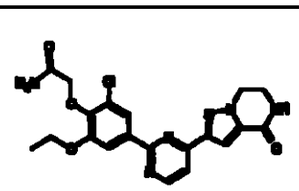
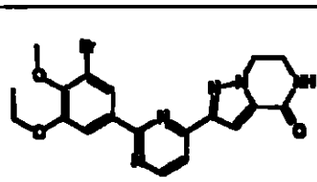
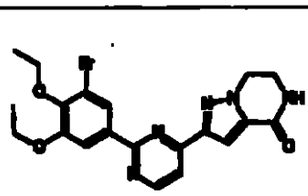
615		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2- il) pirimidin-2-il]fenoxi]-N-fenilacetamida	
616		N-bencil-2-[2-metoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi]acetamida	
617		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi]-N-(2-feniletil)acetamida	
618		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazoto[1,5-a]pirazin-2-il)pirimidin-2-il)fenoxi]-N-(2-metilfenil)acetamida	
619		2-(2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a)pirazin-2-il)pirimidin-2-il]fenoxi]-N-(4-metilfenil)acetamida	
620		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2- il) pirimidin-2-il]fenoxi]-N-(2- . metoxifenil)acetamida	
621		4-[({2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}acetil)amino] benzoato	
622		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N,N-difenilacetamida	
623		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N-1-naftilacetamida	

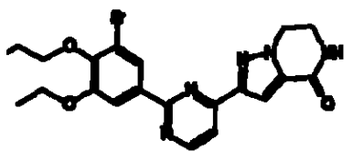
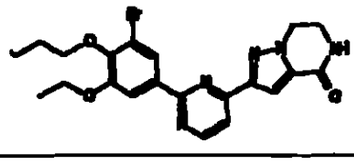
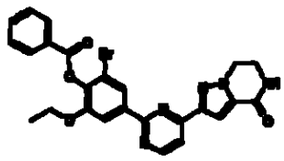
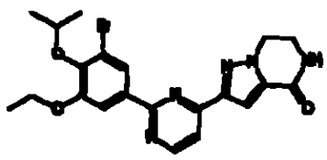
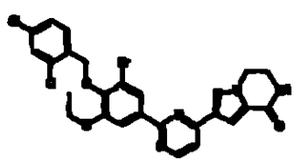
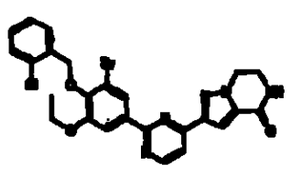
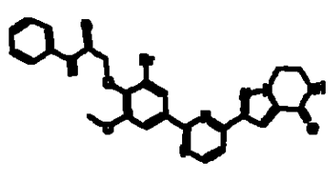
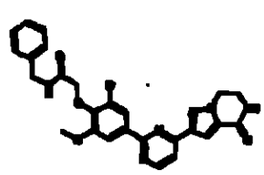
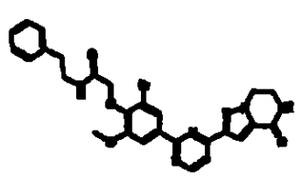
624		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-[3-(trifluorometil)fenil]acetamida	
625		ácido 4-[({2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}acetil)amino] benzoico	
626		2-[2-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}acetamida	
627		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}-N-fenilacetamida	
628		N-bencil-2-{2-etoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a] pirazin-2- il)pirimidin-2-il]fenoxd} acetamida	
629		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2- il) pirimidin-2-il]fenoxi}-N-(2-feniletil)acetamida	
630		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}-N-(2-metilfenil)acetamida	
631		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}-N-(4-metilfenil)acetamida	
632		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il)]fenoxi}-N-(2-metoxifenil)acetamida	

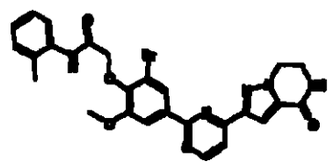
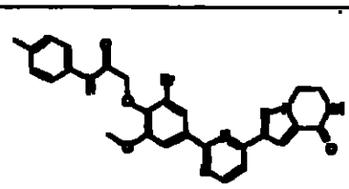
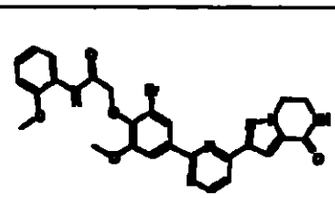
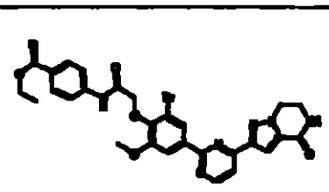
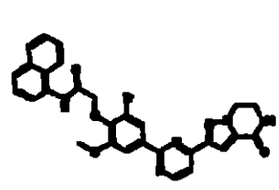
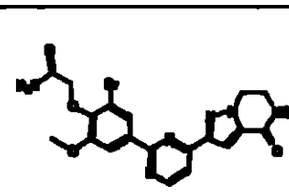
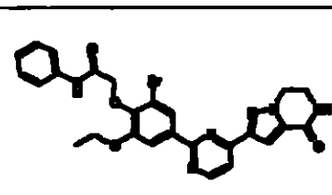
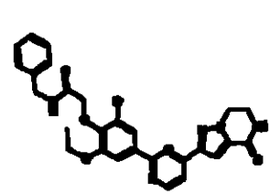
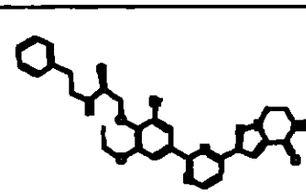
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634		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N-1-naftilacetamida	
635		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N-[3-(trifluorometil)fenil]acetamida	
636		2-[2-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]acetamida	
637		2-[2-(3-cloro-4,5-dimetoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
638		2-[2-(3-cloro-4-etoxi-5-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
639		2-[2-(3-cloro-5-metoxi-4-propoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
640		2-[2-(4-butoxi-3-cloro-5-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
641		2-cloro-6-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil benzoato	

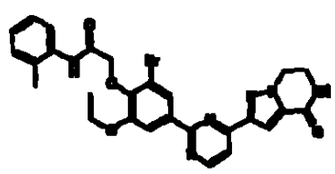
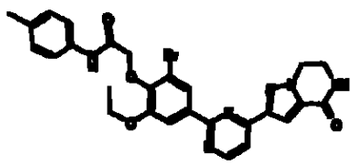
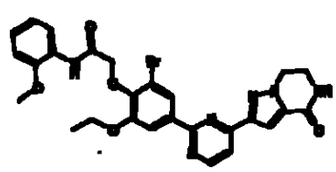
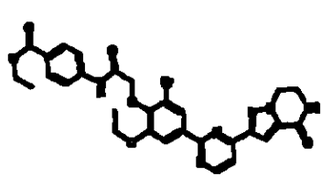
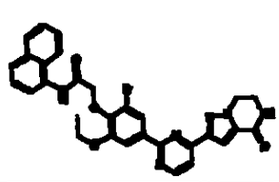
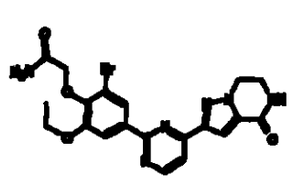
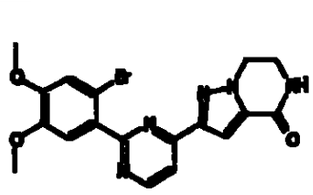
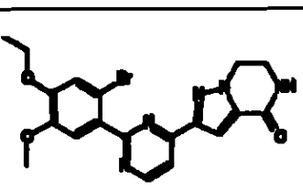
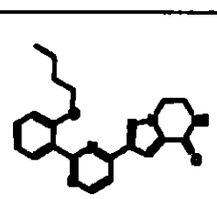
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643		2-{2-[4-(benciloxi)-3-cloro-5-metoxifenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
644		2-(2-{3-cloro-4-[(2-clorobencil)oxi]-5-metoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
645		2-[2-(3-cloro-5-etoxi-4-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
646		2-[2-(3-cloro-4,5-dietoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
647		2-[2-(3-cloro-5-etoxi-4-propoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
648		2-[2-(4-butoxi-3-cloro-5-etoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
649		2-[2-[3-cloro-5-etoxi-4-(2-hidroxietoxi)fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
650		2-cloro-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenilbenzoato	

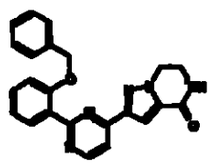
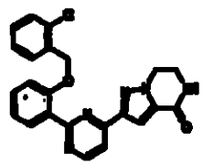
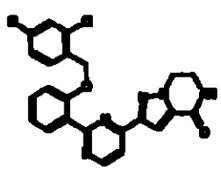
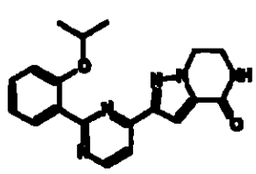
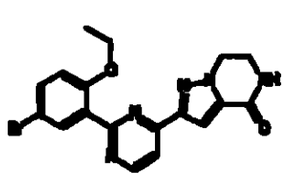
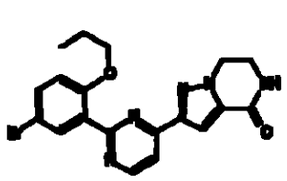
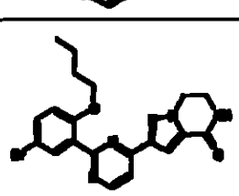
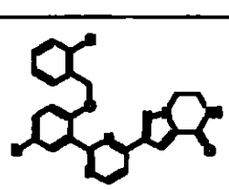
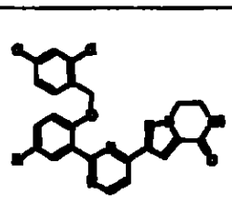
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652		2-{2-[4-(benciloxi)-3-cloro-5-etoxifenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
653		2-(2-{3-cloro-4-[(2,4-diclorobencil)oxi]-5-etoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
654		2-(2-{3-cloro-4-[(2-clorobencil)oxi]-5-etoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
655		ácido 4-({2-cloro-6-etoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi} metil)benzoico	
656		2-[2-(3-bromo-4,5- dimetoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
657		2-[2-(3-bromo-4-etoxi-5-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
658		2-[2-(3-bromo-5-metoxi-4-propoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
659		2-[2-(3-bromo-4-butoxi-5-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

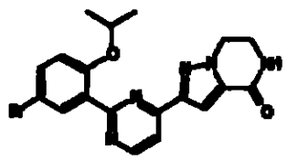
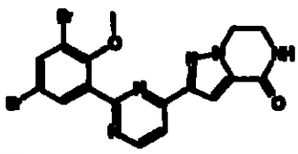
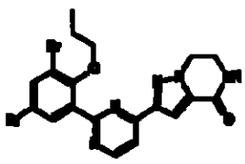
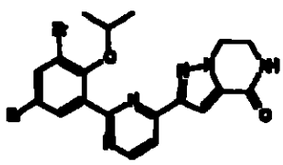
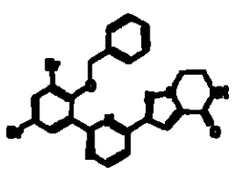
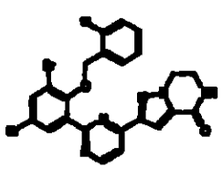
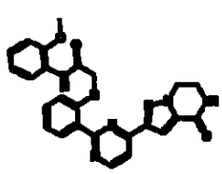
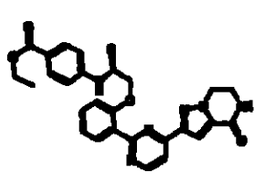
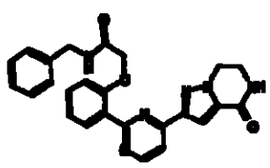
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661		2-[2-(3-bromo-4-isopropoxi-5-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
662		2-(2-{3-bromo-4-[(2,4-diclorobencil) oxi]-5-metoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
663		2-(2-{3-bromo-4-[(2-clorobencil)oxi]-5-metoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
664		2-[2-cloro-6-metoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi]-N-fenilacetamida	
665		2-[2-cloro-6-metoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi]acetamida	
666		2-[2-cloro-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi]acetamida	
667		2-[2-(3-bromo-5-etoxi-4-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
668		2-[2-(3-bromo-4,5-dietoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

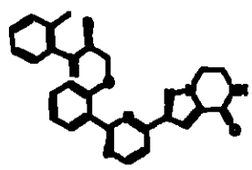
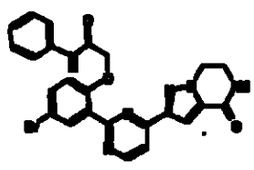
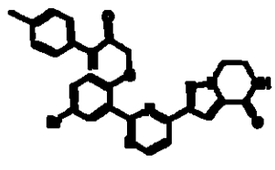
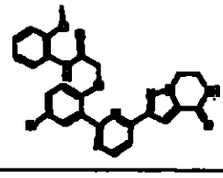
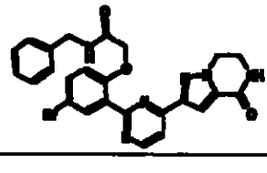
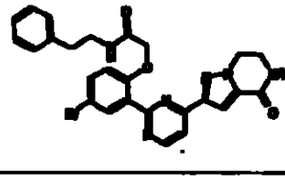
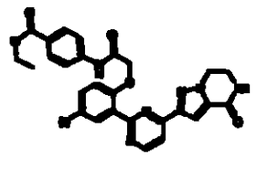
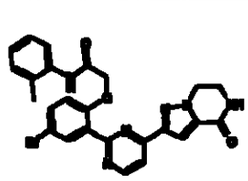
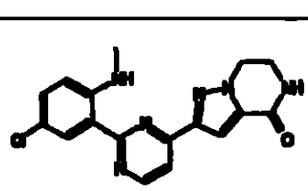
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670		2-[2-(3-bromo-4-butoxi-5-etoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
671		2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenilbenzoato	
672		2[2-(3-bromo-5-etoxi-4-isopropoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
673		2-(2-{3-bromo-4-[(2,4-diclorobencil) oxi]-5-etoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
674		2-(2-{3-bromo-4-[(2-clorobencil)oxi]-5-etoxifenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
675		2-{2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-fenilacetamida	
676		N-bencil-2-{2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi} acetamida	
677		2-{2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-(2-feniletil)acetamida	

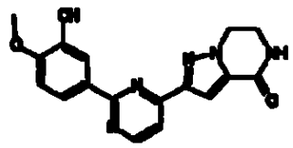
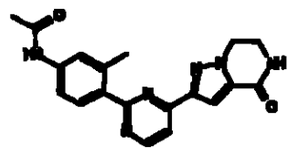
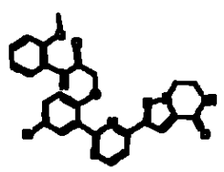
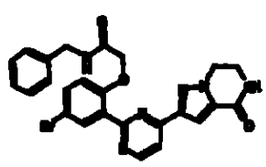
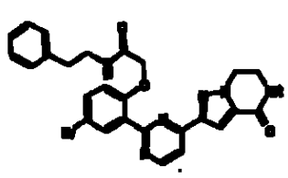
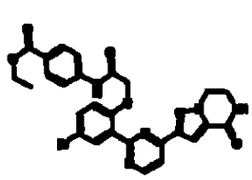
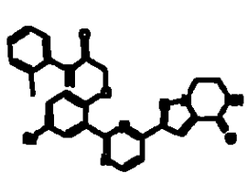
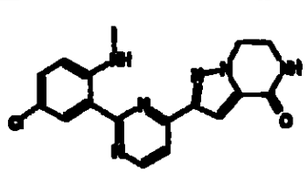
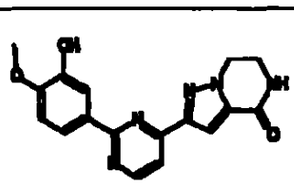
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679		2-{2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-(4- metilfenil)acetamida	
680		2-{2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-(2- metoxifenil)acetamida	
681		etil 4-[({2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi} acetil)amino]benzoato	
682		2-{2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-1- naftilacetamida	
683		2-{2-bromo-6-metoxi-4-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi} acetamida	
684		2-{2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-fenilacetamida	
685		N-bencil-2-{2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi} acetamida	
686		2-{2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-(2- feniletil)acetamida	

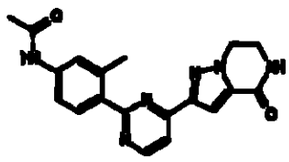
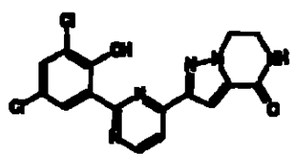
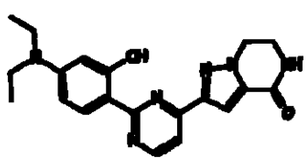
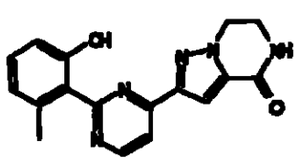
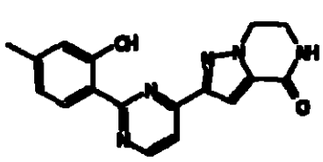
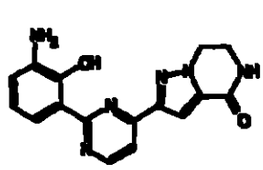
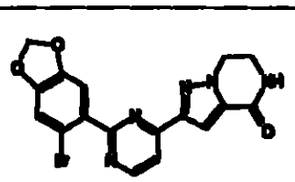
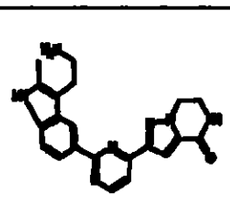
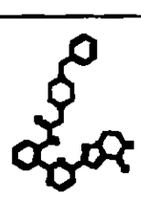
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688		2-{2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-(4- metilfenil)acetamida	
689		2-{2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-(2- metoxifenil)acetamida	
690		etil 4-[([2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi]acetil) amino]benzoato	
691		2-{2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}-N-1- naftilacetamida	
692		2-{2-bromo-6-etoxi-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2- il)pirimidin-2-il]fenoxi}acetamida	
693		2-[2-(2-bromo-4,5-dimetoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
694		2-[2-(2-bromo-4-etoxi-5-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
695		2-[2-(2-butoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

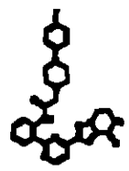
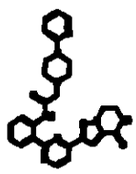
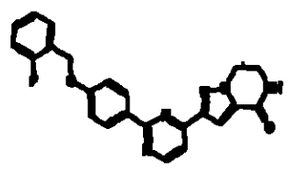
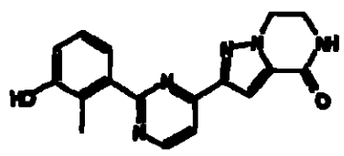
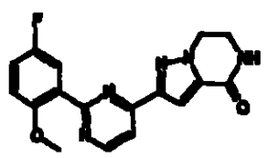
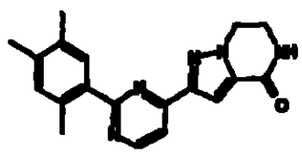
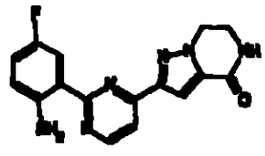
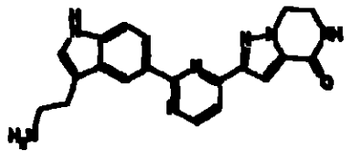
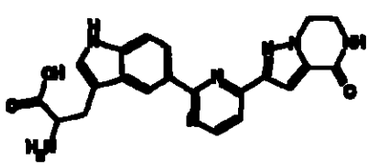
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697		2-(2-{2-[(2-clorobencil)oxi]fenil} pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
698		2-(2-{2-[(2,4-diclorobencil)oxi] fenil} pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
699		2-[2-(2-isopropoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
700		2-[2-(5-bromo-2-etoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
701		2-[2-(5-bromo-2-propoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
702		2-[2-(5-bromo-2-butoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
703		2-(2-{5-bromo-2-[(2-clorobencil)oxi] fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
704		2-(2-(5-bromo-2-[(2,4-diclorobencil) oxi]fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

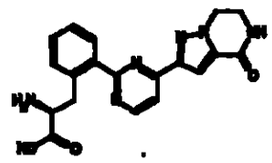
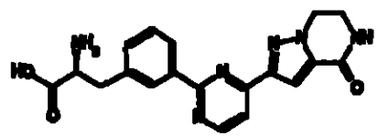
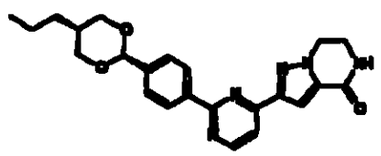
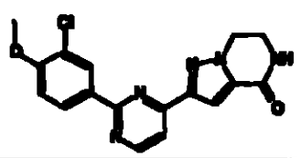
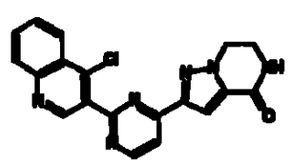
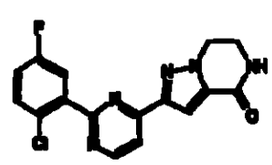
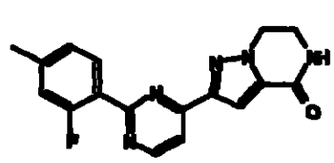
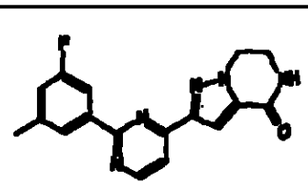
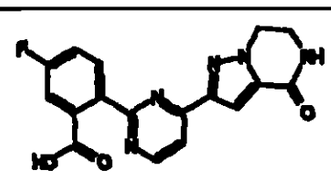
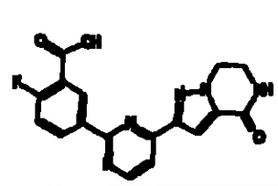
705		2-[2-(5-bromo-2-isopropoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
706		2-[2-(3,5-dibromo-2-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
707		2-[2-(3,5-dibromo-2-propoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
708		2-[2-(3,5-dibromo-2-isopropoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
709		2-[2-[2-(benciloxi)-3,5-dibromofenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
710		2-(2-{3,5-dibromo-2-[(2-clorobencil) oxi] fenil}pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
711		N-(2-metoxifenil)-2-{2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi}acetamida	
712		etil 4-[({2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}acetil)amino] benzoato	
713		N-bencil-2-{2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi}acetamida	

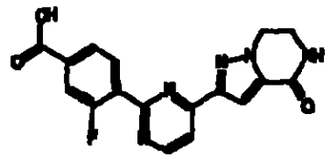
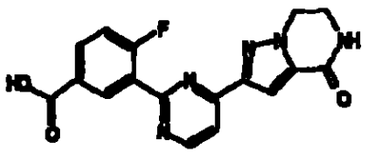
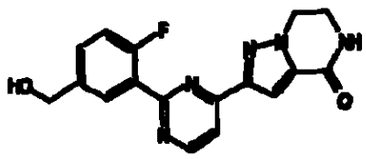
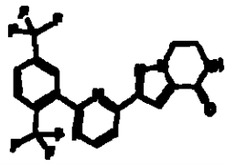
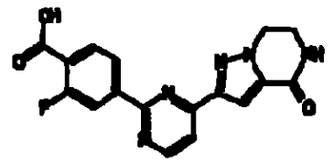
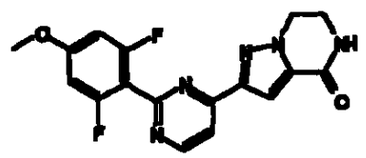
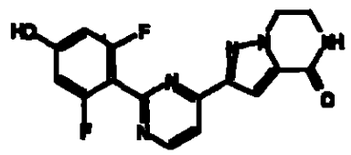
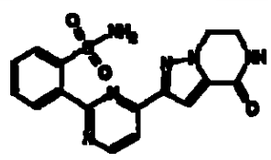
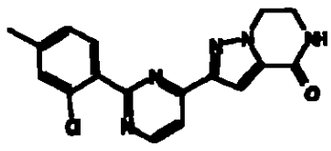
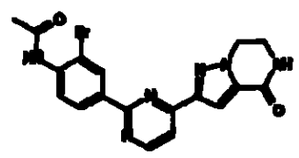
714		N-(2-metilfenil)-2-[2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2- il)pirimidin-2-il]fenoxi]acetamida	
715		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N-fenilacetamida	
716		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N-(4-metilfenil)	
717		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N-(2-metoxifenil)acetamida	
718		N-bencil-2-[4-bromo-2-[4-(4-oxo-4,5,6,7- tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenoxi]acetamida	
719		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]fenoxi]-N-(2-feniletil)acetamida	
720		etil 4-[((4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi)acetil) amino]benzoato	
721		2-[4-bromo-2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenoxi]-N-(2-metilfenil)acetamida	
722		2-[2-[5-cloro-2-(metilamino)fenil] pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

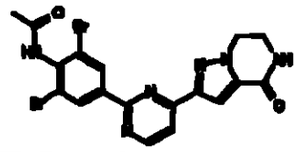
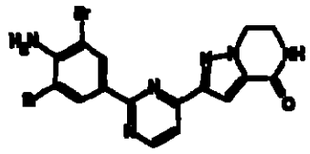
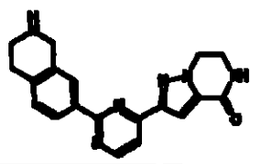
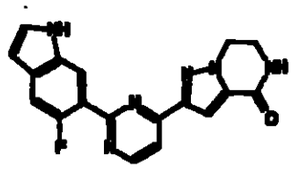
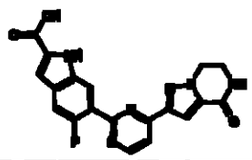
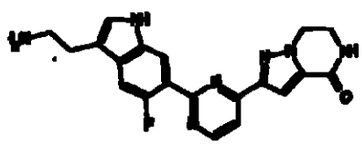
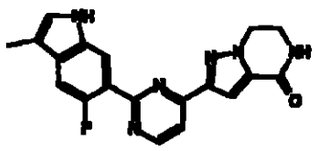
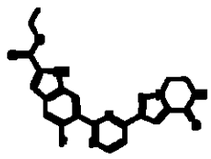
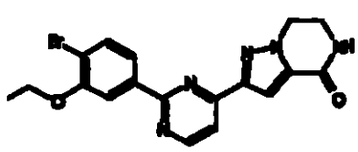
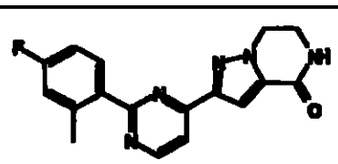
723		2-[2-(3-hidroxi-4-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
724		N-{3-metil-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil}acetamida	
725		2-[2-(2,3-dihidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
726		2-[2-(2,4-dihidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
727		2-[2-(2,6-dihidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
728		2-[2-(2,3,4-trihidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
729		2-[2-(2,4,6-trihidroxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
730		2-[2-(2-hidroxi-5-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
731		2-[2-(2-hidroxi-3-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

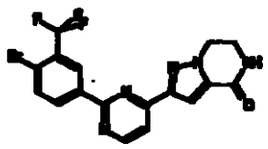
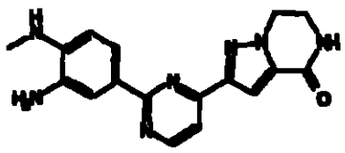
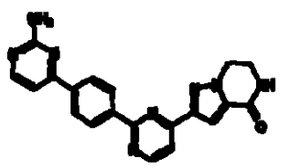
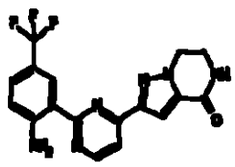
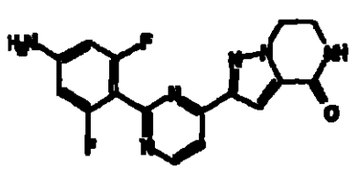
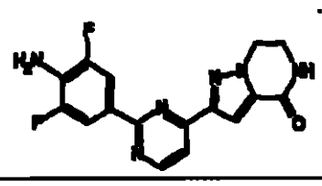
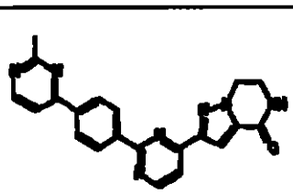
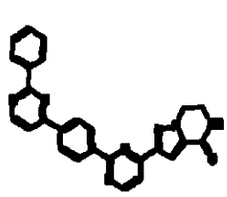
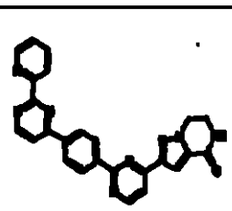
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733		2-[2-(3,5-dicloro-2-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
734		2-[2-[4-(dietilamino)-2-hidroxifenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
735		2-[2-(2-hidroxi-6-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
736		2-[2-(2-hidroxi-4-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
737		2-[2-(3-amino-2-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
738		2-[2-(6-bromo-1,3-benzodioxol-5-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
739		2-[2-[3-(2-aminoetil)-2-metil-1H-indol-5-il]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
740		2-(4-bencilpiperazin-1-il)-N-[2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a] pirazin-2-il)pirimidin-2-il]fenil] acetamida	

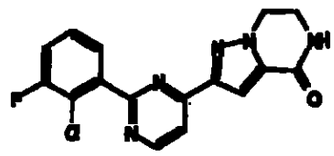
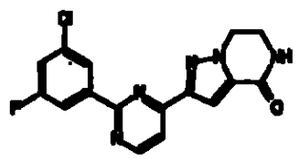
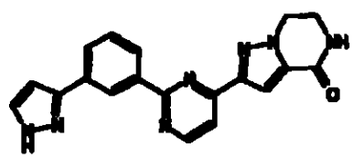
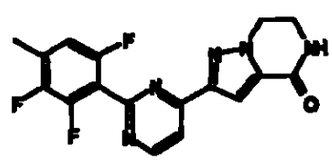
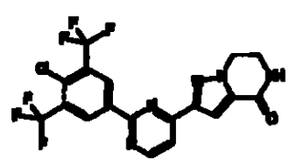
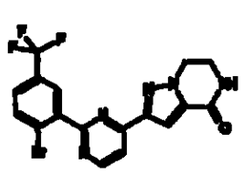
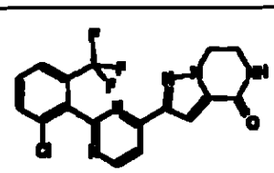
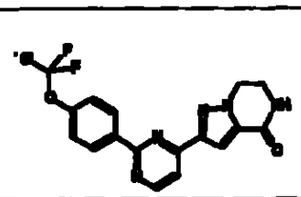
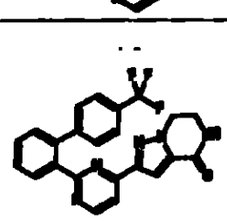
741		2-[4-(4-fluorofenil)piperazin-1-il]-N-(2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] fenil)acetamida	
742		N-{2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il) pirimidin-2-il]fenil}-2-(4-piridin-2-ilpiperazin-1-il)acetamida	
743		2-(2-{4-[(2-fluorobencil)oxi]fenil} pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
744		2-[2-(3-hidroxi-2-metilfenil) pirimidin-4 il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
745		2-[2-(5-fluoro-2-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
746		2-[2-(2, 4, 5-trimetilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
747		2-[2-(2-amino-5-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
748		2-{2-[3-(2-aminoetil)-1H-indol-5-il] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
749		5-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il] triptófano	

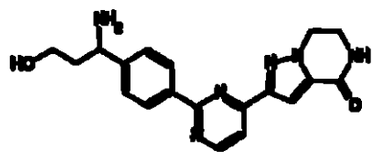
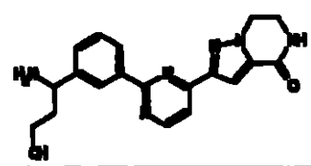
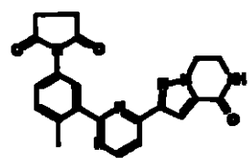
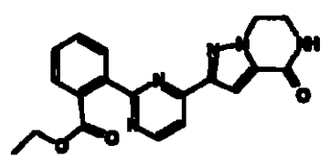
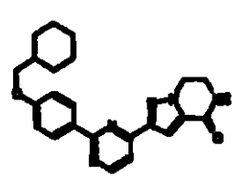
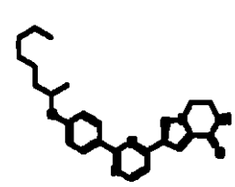
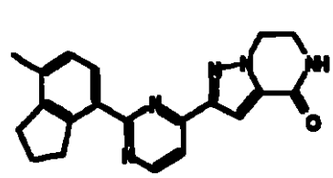
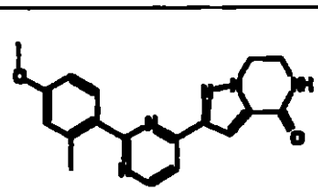
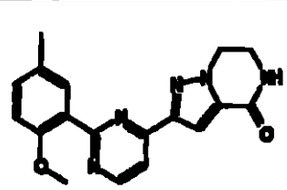
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751		3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]-L-fenilalanina	
752		2-[2-[4-(5-propil-1,3-dioxan-2-il) fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
753		2-[2-(3-cloro-4-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
754		2-[2-(4-cloroquinolin-3-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
755		2-[2-(2-cloro-5-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
756		2-[2-(2-fluoro-4-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
757		2-[2-(3-fluoro-5-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
758		ácido 5-fluoro-2-(4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoico	
759		ácido 2-fluoro-5-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoico	

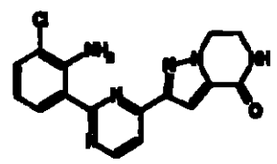
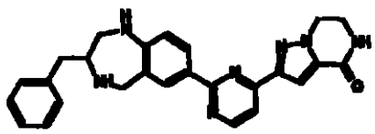
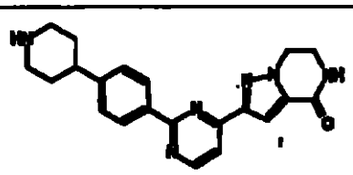
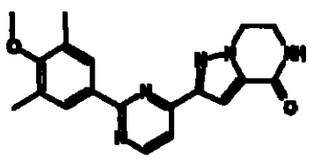
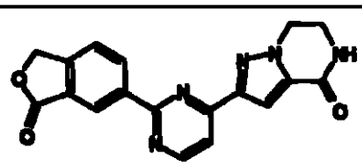
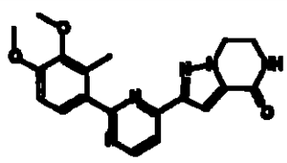
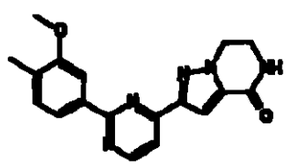
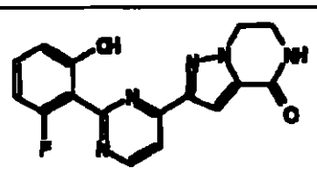
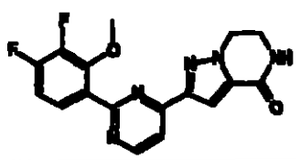
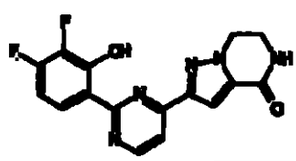
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761		ácido 4-fluoro-3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoico	
762		2-[2-[2-fluoro-5-(hidroximetil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
763		2-[2-[2,5-bis(trifluorometil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
764		ácido 2-fluoro-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoico	
765		2-[2-(2,6-difluoro-4-metoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
766		2-[2-(2,6-difluoro-4-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
767		2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo [1,5-a]pirazin-2-il)pirimidin-2-il]bencenosulfonamida	
768		2-[2-(2-cloro-4-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
769		N-[2-bromo-4-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil]acetamida	

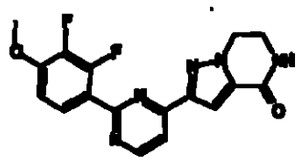
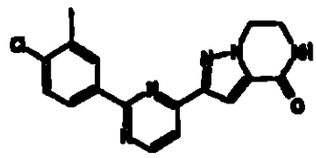
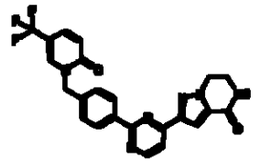
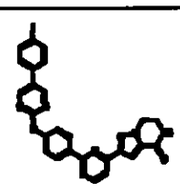
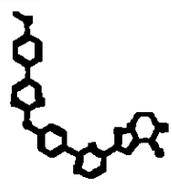
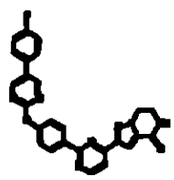
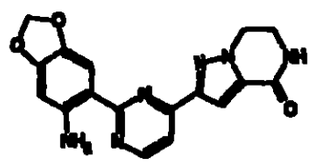
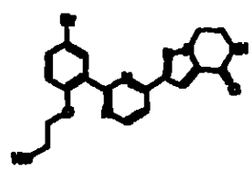
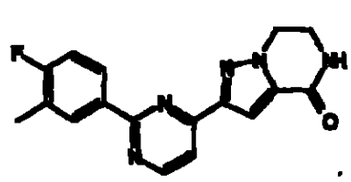
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771		2-[2-(4-amino-3,5-dibromofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
772		2-[2-(1,2,3,4-tetrahidroisoquinolin-7-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
773		2-[2-(5-fluoro-1H indol-6-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
774		ácido 5-fluoro-6-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-1H-indole-2-carboxílico	
775		2-[2-[3-(2-aminoetil)-5-fluoro-1H-indol-6-il]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
776		2-[2-(5-fluoro-3-metil-1H-indol-6-il) pirimidin-4-il]-6,7-dihidropirazolo [1, 5-a]pirazin-4(5H)-ona	
777		etil 5-fluoro-6-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]-1H-indol-2-carboxilato	
778		2-[2-(4-bromo-3-etoxifenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
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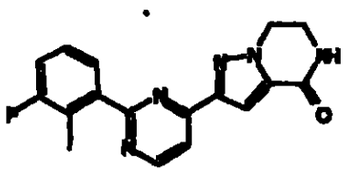
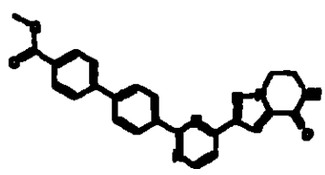
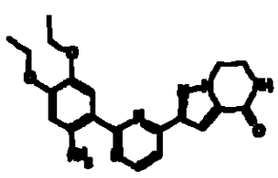
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781		2-{2-[3-amino-4-(metilamino)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
782		2-{2-[4-(2-aminopirimidin-4-il)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
783		2-{2-[2-amino-5-(trifluorometil)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
784		2-[2-(4-amino-2,6-difluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
785		2-[2-(4-amino-3,5-difluorofenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
786		2-{2-[4-(2-metilpirimidin-4-il)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
787		2-{2-[4-(2-fenilpirimidin-4-il)fenil] pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
788		2-{2-[4-(2-piridin-2-ilpirimidin-4-il) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

789		2-[2-(2-cloro-3-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
790		2-[2-(3-cloro-5-fluorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
791		2-[2-[3-(1H-pirazol-3-il)fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
792		2-[2-(2,3,6-trifluoro-4-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
793		2-[2-[4-cloro-3,5-bis(trifluorometil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
794		2-[2-[2-bromo-5-(trifluorometil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
795		2-[2-[2-cloro-6-(trifluorometil)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
796		2-(2-[4-[cloro(difluoro)metoxi]fenil} pirimidin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-(5H)-ona	
797		2-[2-[4'-(trifluorometil)-1,1'-bifenil-2-il] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

798		2-[2-[4-(1-amino-3-hidroxipropil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
799		2-[2-[3-(1-amino-3-hidroxipropil) fenil]pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
800		1-[4-metil-3-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]fenil]pirrolidin-2,5-diona	
801		etil 2-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il) pirimidin-2-il]benzoato	
802		2-[2-[4-(ciclohexilmetoxi)fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
803		2-[2-[4-[(1-metilheptil)oxi]fenil] pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
804		2-[2-(7-metil-2,3-dihidro-1H-inden-4-il)pirimidin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
805		2-[2-(4-metoxi-2-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
806		2-[2-(2-metoxi-5-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

807		2-[2-(2-amino-3-clorofenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
808		2-[2-(3-bencil-2,3,4,5-tetrahidro-1H-1,4- benzodiazepin-7-il)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
809		2-[2-(4-piperidin-4-ilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
810		2-[2-(4-metoxi-3,5-dimetilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
811		2-[2-(3-oxo-1,3-dihidro-2-benzofuran-5-il)pirimidin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
812		2-[2-(3,4-dimetoxi-2-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
813		2-[2-(3-metoxi-4-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
814		2-[2-(2-fluoro-6-hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
815		2-[2-(3,4-difluoro-2-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
816		2-[2-(3,4-difluoro-2- hidroxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

817		2-[2-(2,3-difluoro-4-metoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
818		2-[2-(4-cloro-3-metilfenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
819		2-[2-(4-{[2-oxo-5-(trifluorometil) piridin-1(2H)-il]metil}fenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
820		2-[2-(4-{[5-(4-metilfenil)pirimidin-2-il]oxi}fenil)pirimidin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona	
821		2-[2-(4-{[5-(4-metoxifenil)pirimidin-2-il]oxi}fenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
822		2-[2-(4-{[5-(4-fluorofenil)pirimidin-2-il]oxi}fenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
823		2-[2-(6-amino-1,3-benzodioxol-5-il) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
824		2-{2-[5-bromo-2-(2-hidroxietoxi) fenil]pirimidin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
825		2-[2-(4-fluoro-3-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

826		2-[2-(3-fluoro-2-metilfenil)pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	
827		metil 4'-[4-(4-oxo-4,5,6,7-tetrahidropirazolo[1,5-a]pirazin-2-il)pirimidin-2-il]-1,1'-bifenil-4-carboxilato	
828		2-[2-(2-amino-4, 5-dietoxifenil) pirimidin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona	

Notas:

a) Las denominaciones químicas se generaron con software ACD/Name.

b) El compuesto inhibidor de MK-2 puede indicarse con un disolvente, tal como, por ejemplo, trifluoroacetato, con el cual puede formar una sal. Tanto la sal como las formas base de cada compuesto se incluyen en la presente invención.

[00039] En una incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que se enumera en Tabla I.

[00040] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que se enumera en Tabla 1 o en Tabla 2.

[00041] En todavía otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que se enumera en Tabla 2.

[00042] Se prefiere que el compuesto inhibidor de MK-2 sea uno con un valor IC_{50} para la inhibición de MK-2 que es menor de 1. A manera de ejemplo, esto incluiría los compuestos en Tabla I numerados 1 - 56. Todavía más preferido es un valor IC_{50} MK-2 que es menor de 0.5 (ejemplos de estos compuestos incluyen los compuestos en Tabla I numerados 1 - 32), todavía más preferido es un valor menor de 0.1 (ejemplos de estos compuestos incluyen los compuestos en la Tabla I numerados 1 - 7).

[00043] En una incorporación de la presente invención, el compuesto

inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto cuando Z^2 y Z^3 son ambos nitrógeno, R^4 es distinto de pirrol o, de manera opcional, cuando Z^4 y Z^5 son ambos nitrógeno y R^a es un anillo Q, Q^2 es distinto de nitrógeno.

[00044] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a se selecciona de un anillo M o un anillo Q.

[00045] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a un anillo M.

[00046] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a es un anillo M en donde anillo M es un anillo de piridina o pirimidina aromática, en donde M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si M^2 y/o M^6 es carbono, el carbono de sustituye con $(L)_nR^1$.

[00047] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a es un anillo M en donde anillo M es un anillo de piridina o pirimidina aromática, en donde M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si M^2 y/o M^6 es carbono, el carbono de sustituye con $(L)_nR^1$; y

[00048] R^3 y R^4 se unen de manera opcional para formar un anillo de 5, 6, 7, u 8 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C que es mono- o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

[00049] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a es un anillo M en donde anillo M es un anillo de piridina o pirimidina aromática, en donde M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 y M^6 se seleccionan independientemente de carbono y

nitrógeno y, si carbono, el carbono de sustituye con $(L)_nR^1$; y

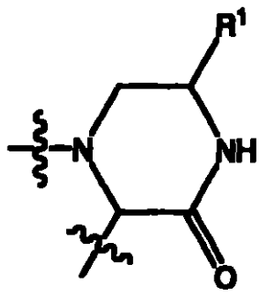
[00050] R^3 y R^4 se unen de manera opcional para formar un anillo de 6 ó 7 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, C=O, C que es mono- o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

[00051] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a es un anillo M, en donde anillo M es un anillo de piridina o pirimidina aromática, en donde M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono de sustituye con $(L)_nR^1$; y

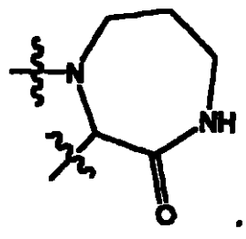
[00052] R^3 y R^4 se unen de manera opcional para formar un anillo de 6 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, C=O, C que es mono- o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

[00053] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a es un anillo M en donde anillo M es un anillo de piridina o pirimidina aromática, en donde M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono de sustituye con $(L)_nR^1$; y

R^3 y R^4 se unen opcionalmente para formar un anillo que se selecciona de:



, y



.

[00054] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a es un anillo M, en donde anillo M es un anillo de piridina aromática, en

donde M^1, M^3, M^4 y M^6 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 es nitrógeno.

[00055] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^8 es un anillo M, en donde anillo M es un anillo de pirimidina aromática, en donde M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 y M^8 son nitrógeno.

[00056] En otra incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^8 es un anillo M en donde anillo M es un anillo de piridina aromática, en donde:

M^1, M^3, M^4 y M^6 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 es nitrógeno;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, hidroxilo, C_1-C_6 alcoxi, C_2-C_6 alquenil-R^{11}, C_1-C_6 alcoxi-R^{11}, COR^{17}, COR_6, CO_2R_6, $CONHR_6$, $N(R^8)_2$, amino C_1-C_4 alquilo, hidroxi C_1-C_4 alquilo, amino, amino C_1-C_4 alquil-R^7, C_1-C_6 alquil-NHR^7, carbonitrilo, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_6 alquilo, NR^8R^9-C_1-C_6 alquilo, nitro, ciano, O-R^{10}, C_1-C_4 alquil-OR^{10}, C_1-C_6 alquil-COR^{11}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, o C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, mono- y bicíclico cicloalquilo se sustituyen opcionalmente con uno o más de los grupos definidos por R^{12};

R^7, R^8, se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, arilo, y arilalquilo, en donde arilo y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^9, R^{10} se seleccionan cada uno independientemente de -H, hidroxilo, C_1-C_6 alquilo, C_1-C_6 alquil-R^{17}, C_1-C_6 alquil-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alquil-CO_2R^{16}, C_1-C_6 alquil-CONH-R^{16}, C_1-C_6 alquil-$CON(R^{16})_2$, hidroxi

C_1-C_4 alquilo, halo C_1-C_4 alcoxi, halo C_1-C_4 alquilo, $Si(R^{13})_2R^{17}$, arilo, heteroarilo, heterociclilo, arilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxilo, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo, y heterociclilalquilo, en donde heterociclilo, heteroarilalquilo, y heterociclilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, hidroxilo, oxo, C_1-C_6 alquilo, hidroxil C_1-C_6 alquil-R^{11}, C_1-C_{10} alcoxi, amino, amino C_1-C_4 alquil-R^7, NHR^7, $N(R^7)_2$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NHR^8R^9, C_1-C_6 alquil-$N(R^8)_2$, C_1-C_6 alquil-R^{11}, C_1-C_6 alquil-$CO_2R^7R^{11}$, C_1-C_6 alcoxi-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_6 alquil-SR^{10}, halo, halo C_1-C_4 alquilo, halo C_1-C_4 alcoxi, hidroxi C_1-C_4 alquilo, hidroxi C_1-C_4 alcoxi, arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, y heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{13} y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, COR^{23}, y arilo;

R^{15}, R^{16} se seleccionan cada uno independientemente de -H, arilo, arilalquilo, en donde arilo, arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alquil-R^{19}, NHR^{19}, arilo, heteroarilalquilo, y heterociclilalquilo, en donde arilo se sustituye opcionalmente con uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, hidroxilo, C_1-C_{10} alquilo, C_1-C_{10} alcoxi, amino, amino C_1-C_6 alquilo, $N(R^{19})_2$, C_1-C_6 alquil-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, y heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen opcionalmente con uno o más de

los grupos definidos por R^{24};

y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, heteroarilo, heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan cada uno independientemente de -H y C_1-C_6 alquilo;

R^{23} se selecciona de -H y C_1-C_6 alquilo;

R^{24} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, CO_2R^{29}, halo, y halo C_1-C_4 alquilo;

R^{29} se selecciona de -H, y C_1-C_6 alquilo;

R^{30} se selecciona de -H, arilo, heteroarilo, heterociclilo, alquilarilo, arilalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H y halo; y

R^2, R^3, R^4, R^{37} y R^{38} se seleccionan cada uno independientemente de un grupo R^1.

[00057] En una incorporación de la presente invención, el compuesto inhibidor de MK-2 es uno que tiene la estructura de fórmula I, excepto que R^a es un anillo M en donde anillo M es un anillo de pirimidina aromática, en donde:

M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 y M^6 son nitrógeno;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, hidroxilo, C_1-C_6 alcoxi, C_2-C_6 alquenil-R^{11}, C_1-C_6 alcoxi-R^{11}, COR^{17}, COR_6, CO_2R_6, $CONHR_6$, $N(R^8)_2$, amino C_1-C_4 alquilo, hidroxi C_1-C_4 alquilo, amino, amino C_1-C_4 alquil-R^7, halo C_1-C_4 alquilo, C_1-C_6 alquil-NHR^7, carbonitrilo, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_6 alquilo, NR^8R^9-C_1-C_6 alquilo, nitro, ciano, O-R^{10}, C_1-C_4 alquil-OR^{10}, C_1-C_6 alquil-COR^{11}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo,

alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, o C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, mono- y bicíclico cicloalquilo se sustituyen opcionalmente con uno o más de los grupos definidos por R^{12};

R^7, R^8, se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, arilo, y arilalquilo, en donde arilo y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^9, R^{10} se seleccionan cada uno independientemente de -H, hidroxilo, C_1-C_6 alquilo. C_1-C_6 alquil-R^{17} C_1-C_6 alquil-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alquil-CO_2R^{16}, C_1-C_6 alquil-$CONH$-R^{16}, C_1-C_6 alquil-$CON(R^{16})_2$, hidroxi C_1-C_4 alquilo, halo C_1-C_4 alcoxi, halo C_1-C_4 alquilo, $Si(R^{13})_2R^{17}$, arilo, heteroarilo, heterociclilo, arilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxilo, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo, y heterociclilalquilo, en donde heterociclilo, heteroarilalquilo, y heterociclilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, hidroxilo, oxo, C_1-Ce alquilo, hidroxil C_1-C_6 alquil-R^{11}, C_1-C_{10} alcoxi, amino, amino C_1-C_4 alquil-R^7 NHR^7, $N(R^7)_2$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NHR^8R^9, C_1-C_6 alquil-$N(R^8)_2$, C_1-C_6 alquil-R^{11}, C_1-C_6 alquil-$CO_2R^7R^{11}$, C_1-C_6 alcoxi-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_6 alquil-SR^{10}, halo, halo C_1-C_4 alquilo, halo C_1-C_4 alcoxi, hidroxi C_1-C_4 alquilo, hidroxi C_1-C_4 alcoxi, arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, y heterociclilalquil , y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{13}y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-

C_6 alquilo, COR^{23}, y arilo;

R^{15}, R^{16} se seleccionan cada uno independientemente de -H, arilo, arilalquilo, en donde arilo, arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alquil-R^{19}, NHR^{19}, arilo, heteroarilalquilo, y heterociclilalquilo, en donde arilo se sustituye opcionalmente con uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, hidroxilo, C_1-C_{10} alquilo, C_1-C_{10} alcoxi, amino, amino C_1-C_6 alquil-$N(R^{19})_2$, C_1-C_6 alquil-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, y heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, heteroarilo, heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan cada uno independientemente de -H y C_1-Ce alquilo;

R^{23} se selecciona de -H y C_1-C_6 alquilo;

R^{24} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, CO_2R^{29}, halo, y halo C_1-C_4 alquilo;

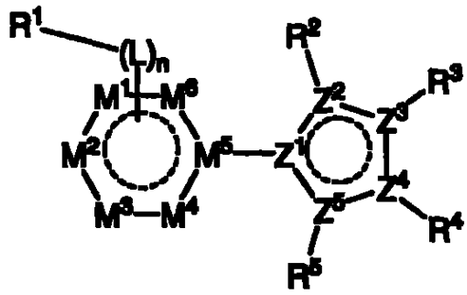
R^{29} se selecciona de -H, y C_1-C_6 alquilo;

R^{30} se selecciona de -H, arilo, heteroarilo, heterociclilo, alquilarilo, arilalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H y halo; y

R^2, R^3, R^4, R^{37} y R^{38} se seleccionan cada uno independientemente de un grupo R^1.

[00058] En otra incorporación, el presente compuesto inhibidor de MK-2 tiene la estructura mostrada en fórmula III: Fórmula III:



en donde:

las líneas discontinuas indican enlaces sencillos o dobles;

Z^2 y Z^3 son nitrógeno, Z^1, Z^4 y Z^5 son carbono, y se unen con Z^2 y Z^3 para formar un anillo pirazol;

donde las líneas discontinuas indican enlaces sencillos o dobles;

M^1, M^3 y M^4 es carbono y se sustituye con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2 y M^6 se selecciona independientemente de nitrógeno y carbono, y si carbono, es no sustituido o sustituido con $(L)_nR^1$;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C2-C_6 alquinilo, hidroxilo, C_1-C_6 alcoxi, C_2-C_6 alquenil-R^{11}, C_1-C_6 alcoxi-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alquilo, hidroxi C_1-C_4 alquilo, amino, amino C_1-C_4 alquil-R^7, halo C_1-C_4 alquilo, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-$N(R^7)_2$, carbonitrilo, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_6 alquilo, NR^8R^9-C_1-C_6 alquilo, nitro, ciano, O-R^{10}, C_1-C_4 alquil-OR^{10}, C_1-C_6 alquil-COR^{11}, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, o C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, mono- y bicíclico cicloalquilo se sustituyen opcionalmente con uno o más de los grupos definidos por R^{12};

R^7 y R^8 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, arilo, y arilalquilo, en donde arilo y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^9 y R^{10} se seleccionan cada uno independientemente de -H, hidroxilo, C_1-C_6 alquilo, C_1-C_6 alquil-R^{17}, C_1-C_6 alquil-NH_2R^{13}, CO_2R^{16},

COR^{17}, C_1-C_6 alquil-CO_2R^{16}, C_1-C_6 alquil-$CONH$-R^{16}, C_1-C_6 alquil-$CON(R^{16})_2$, hidroxi C_1-C_4 alquilo, halo C_1-C_4 alcoxi, halo C_1-C_4 alquilo, $Si(R^{13})_2R^{17}$, arilo, heteroarilo, heterociclilo, arilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-Ce alquilo, C_1-C_6 alcoxi, hidroxilo, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo, y heterociclilalquilo, en donde heterociclilo, heteroarilalquilo, y heterociclilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, hidroxilo, oxo, C_1-C_6 alquilo, hidroxil C_1-C_6 alquil-R^{11}, C_1-C_{10} alcoxi, amino, amino C_1-C_4 alquil-R^7, NHR^7, $N(R^7)_2$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NHR^8R^9, C_1-C_6 alquil-$N(R^8)_2$, C_1-C_6 alquil-R^{11}, C_1-C_6 alquil-$CO_2R^7R^{11}$, C_1-C_6 alcoxi-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11} SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$ C_1-C_6 alquil-SR^{10}, halo, halo C_1-C_4 alquilo, halo C_1-C_4 alcoxi, hidroxi C_1-C_4 alquilo, hidroxi C_1-C_4 alcoxi, arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, y heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen opcionalmente con uno o más de los grupos definidos por R^{18};

R^{13} y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, COR^{23}, y arilo;

R^{15} y R^{16} se seleccionan cada uno independientemente de -H, arilo, arilalquilo, en donde arilo, arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alquil-R^{19}, NHR^{19}, arilo, heteroarilalquilo, y heterociclilalquilo, en donde arilo se sustituye opcionalmente con uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, hidroxilo, C_1-C_{10} alquilo, C_1-C_{10} alcoxi, amino, amino C_1-C_6 alquilo, $N(R^{19})_2$, C_1-C_6 alquil-$N(R^{19})_2$, CO_2R^{23}, SR^{21},

halo, halo C_1-C_4 alquilo, arilo, heteroarilo, y heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, heteroarilo, heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan cada uno independientemente de -H y C_1-C6 alquilo;

R^{23} se selecciona de -H y C_1-C_6 alquilo;

R^{24} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, CO_2R^{29}, halo, y halo C_1-C_4 alquilo;

R^{29} se selecciona de -H, y C_1-C_6 alquilo;

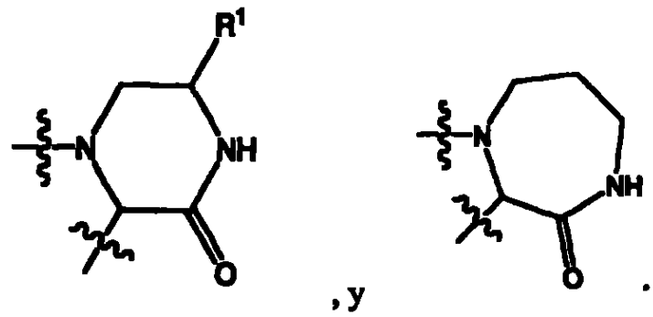
R^{30} se selecciona de -H, arilo, heteroarilo, heterociclilo, alquilarilo, arilalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, y arilalquilo, se sustituyen opcionalmente con uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H y halo;

R^2, R^3, R^4, R^{37} y R^{38} se seleccionan cada uno independientemente de un grupo R^1;

n es 0; y

R^3 y R^4 se unen opcionalmente para formar una estructura que se selecciona de:



, y .

[00059] Los compuestos inhibidores de MK-2 que se describen en fórmulas I-III, y en Tablas I y II pueden preparase por lo métodos que se

describen en los Ejemplos siguientes. Los compuestos no descritos específicamente en los Ejemplos pueden elaborarse por referencia a los métodos usados en los Ejemplos, pero con la sustitución de compuestos de partida que son apropiados para el compuesto que se desea.

[00060] La presente invención incluye además un método de inhibir proteína cinasa-2 activada por protenina cinasa activada por mitógenos, método que comprende poner en contacto una proteína cinasa-2 activada por protenína cinasa activada por mitógenos con uno o más de cualquiera de los compuestos inhibidores de MK-2 descritos aquí. En una incorporación, la puesta en contacto de MK-2 con un compuesto inhibidor de MK-2 tiene lugar en una célula. La célula puede ser una de cualquier tipo de organismo, pero es preferiblemente una célula animal. La puesta en contacto puede ocurrir *in vitro* o *in vivo*, y la célula puede ser una célula viva, o puede ser no viva. Cuando la puesta en contacto se lleva a cabo *in vitro*, la célula puede unirse a otras células, o puede ser una célula única, o aglomeración de células en suspensión o en un medio sólido. Cuando la puesta en contacto se lleva a cabo *in vivo*, el compuesto inhibidor de MK-2 puede administrarse como se describe más adelante.

[00061] En una incorporación, la presente invención ofrece un método de prevenir o tratar una enfermedad o trastorno modulado por MK-2 en un individuo, método que comprende poner en contacto una proteína cinasa-2 activada por protenína cinasa activada por mitógenos en un individuo con uno cualquiera o más de los compuestos inhibidores de MK-2 que se describen aquí. Un compuesto inhibidor de MK-2 preferido para el presente método es uno que tiene la estructura descrita por fórmula I. En otra incorporación preferida, el compuesto inhibidor de MK-2 es uno que tiene la estructura descrita por fórmula II.

[00062] La presente invención también un método de inhibir proteína cinasa-2 activada por protenína cinasa activada por mitógenos en un individuo necesitado de tal inhibición, método que comprende administrar al individuo uno cualquiera o más de los compuestos inhibidores de MK-2 descritos aquí.

[00063] De igual manera la presente invención incluye un método de prevenir o tratar una enfermedad o trastorno mediado por TNFα en un individuo, método que comprende administrar al individuo una cantidad efectiva de uno cualquiera o más de los compuestos inhibidores de MK-2 descritos aquí. En una incorporación preferida, el individuo es uno que necesita de tal prevención o tratamiento.

[00064] Los presentes métodos pueden llevarse a la práctica mediante la administración de uno cualquiera o más de los presentes compuestos inhibidores de MK-2. Se prefiere que el compuesto inhibidor de MK-2 sea uno que tenga una IC_{50} MK-2 de menos de alrededor de 10 μM, en un análisis *in vitro* de la actividad inhibidora de MK-2, más preferido es un compuesto que tenga una IC_{50} de MK-2 de menos de alrededor de 1.0 μM, todavía más preferido es un compuesto que tenga una IC_{50} MK-2 de menos de alrededor de 0.5 μM.

[00065] Debe entenderse que las formas base, sales, sales farmacéuticamente aceptables, y profármacos de los compuestos que se describen aquí, así como formas isoméricas, tautómeros, mezclas racémicas de los compuestos, y similares, las cuales tienen la misma o similar actividad que los compuestos que se describen, tienen que considerarse incluidos en la descripción del compuesto.

[00066] La actividad inhibidora de MK-2 de cualquiera de los compuestos descritos aquí puede determinarse por uno cualquiera de varios métodos que son bien conocidos por los expertos en el arte de las pruebas de la actividad enzimática. Un método tal se describe en detalle en la sección Métodos Generales de los Ejemplos. Además, la eficacia de uno cualquiera de los presentes compuestos inhibidores de MK-2 en aplicaciones terapéuticas puede determinarse probando la inhibición de la producción TNFα en un cultivo de células y en análisis con modelos animales. En general, se prefiere que los compuestos inhibidores de MK-2 de la presente invención sean capaces de inhibir la producción y/o la liberación de TNFα en cultivos de células y en modelos animales.

[00067] En el presente método, los compuestos inhibidores de MK-2 que

se han descrito aquí pueden usarse como inhibidores de MAPKAP cinasa-2. Cuando esta inhibición tiene una finalidad terapéutica, uno o más de los presentes compuestos inhibidores de MK-2 pueden administrarse a un individuo necesitado de la inhibición de MK-2. Tal como se emplea aquí, un "individuo necesitado de la inhibición de MK-2" es un individuo que tiene, o que se encuentra de riesgo de contraer una enfermedad o trastorno mediado por TNFα. Las enfermedades o trastornos mediados por TNFα se describen con más detalle a continuación.

[00068] Como se describe más arriba, en una incorporación del presente método, un individuo necesitado de prevención o tratamiento de una enfermedad o trastorno mediado por TNFα se trata con uno o más de los presentes compuestos inhibidores de MK-2. En una incorporación, el individuo se trata con una cantidad efectiva del compuesto inhibidor de MK-2. La cantidad efectiva puede ser una cantidad que es suficiente para prevenir o tratar la enfermedad o desorden mediado por TNFα.

[00069] El compuesto inhibidor de MK-2 que se emplea en el método en cuestión puede ser cualquier compuesto inhibidor de MK-2 que se describe aquí.

[00070] En el método en cuestión, el compuesto inhibidor de MK-2 puede usarse en cualquier cantidad que sea una cantidad efectiva. No obstante, se prefiere que la cantidad del compuesto inhibidor de MK-2 que se administra se encuentre en un rango de alrededor de 0.1 mg/día por kilogramo (kg) del compuesto en cuestión a alrededor de 1500 mg/día/kg. Es más preferido que la cantidad del compuesto esté en un rango de alrededor de 1 mg/día/kg a alrededor de 500 mg/día/kg. Una cantidad que esté en un rango de alrededor de 10 mg/día/kg a alrededor de 400 mg/día/kg es todavía más preferida.

[00071] Cuando el término "alrededor de" se usa aquí en relación con una cantidad posológica del compuesto inhibidor de MK-2, hay que entender que significa una cantidad que está en ± 10% en peso de la cantidad o rango que se describe. A modo de ejemplo, "alrededor de 0.1 -10 mg/día" incluye todas las dosificaciones entre 0.9 a 11 mg/día.

[00072] En una incorporación de la presente invención, se provee una composición terapéutica que contiene por lo menos uno de los compuestos inhibidores de MK-2 que se describen aquí. Una composición terapéutica preferida contiene una cantidad terapéuticamente efectiva de un compuesto que se describe por fórmula I. En otra incorporación, una composición terapéutica preferida es una que tiene un compuesto inhibidor de MK-2 que se describe por fórmula II.

[00073] En otra incorporación de la presente invención, una composición farmacéutica que contiene uno o más de los presentes inhibidores de MK-2 puede administrarse a un individuo para la prevención o tratamiento de una enfermedad o trastorno mediado por TNFα. La composición farmacéutica incluye un inhibidor de MK-2 de la presente invención y un vehículo farmacéuticamente aceptable. Un inhibidor preferido de MK-2 para uso en la composición farmacéutica se describe por fórmula I. En otra incorporación, una composición farmacéutica preferida es una que tiene un compuesto inhibidor de MK-2 que se describe por fórmula II.

[00074] En otra incorporación, puede producirse un estuche que es apropiado para uso en la prevención o tratamiento de una enfermedad o trastorno mediado por TNFα. El estuche comprende una formulación farmacéutica que comprende por lo menos uno de los inhibidores de MK-2 que se describe aquí en una cantidad que comprende una cantidad terapéuticamente efectiva.

[00075] Tal como se emplea aquí, una "cantidad efectiva" significa la dosis o cantidad efectiva a administrarse a un paciente y la frecuencia de administración al individuo, que se determina fácilmente por una persona de habilidad corriente en el arte, mediante el uso de técnicas conocidas y observando los resultados obtenidos bajo circunstancias análogas. La dosis o cantidad efectiva a administrarse a un paciente y la frecuencia de administración al individuo puede determinarse fácilmente por una persona de habilidad corriente en el arte mediante el uso de técnicas conocidas y observando los resultados obtenidos bajo circunstancias análogas. Al determinar la cantidad efectiva o dosis, el médico que tiene a cargo el

diagnóstico considerará un número de factores, incluidos pero no limitados a, la potencia y duración de la acción de los compuestos empleados, la naturaleza y gravedad de la enfermedad por tratar, así como el sexo, edad, peso, salud general y grado de reacción individual del paciente por tratar, y otras circunstancias relevantes.

[00076] La expresión "terapéuticamente efectiva" indica la capacidad de un agente para prevenir, o mejorar, la gravedad del trastorno, impidiendo al mismo tiempo efectos colaterales adversos, asociados típicamente con terapias alternativas. La expresión "terapéuticamente efectiva" tiene que entenderse equivalente la expresión "efectiva para el tratamiento, prevención, o inhibición", y las dos tienen como finalidad calificar la cantidad del compuesto inhibidor de MK-2 para uso en terapia que logrará el objetivo de la mejora en la gravedad del dolor e inflamación y la frecuencia de incidencia durante el tratamiento, evitando al mismo tiempo efectos colaterales adversos, asociados típicamente con terapias alternativas.

[00077] Los expertos en el arte observarán que también pueden determinarse dosificaciones con la guía de Goodman & Goldman's The Pharmacological Basis of Therapeutics. Ninth Edition (1996), Appendix II, páginas 1707-1711.

[00078] La frecuencia de la dosis dependerá de la semivida de los componentes activos de la composición. Si las moléculas activas tienen una semivida corta (por ejemplo, de alrededor de 2 a 10 horas) puede ser necesario administrar una o más dosis por día. Alternativamente, si las moléculas activas tienen una semivida prolongada (por ejemplo, de alrededor de 2 a alrededor de 15 días) puede ser únicamente necesario administrar una dosificación una vez por día, por semana, o incluso una vez cada 1 ó 2 meses. Una frecuencia de dosificación preferida es administrar las cantidades posológicas descritas más arriba a un individuo una vez al día.

[00079] Las dosificaciones diarias pueden variar dentro de límites amplios y se ajustarán a los requerimientos individuales en cada caso particular. En

general, para administración a adultos, una dosificación diaria apropiada se ha descrito más arriba, aunque los límites que se identificaron como preferidos pueden excederse, si se estima conveniente. La dosificación diaria puede administrarse como una dosificación única o en dosificaciones divididas.

[00080] Para los efectos de calcular y expresar una frecuencia de dosificación, todas las dosificaciones que se expresan aquí se calculan en una base cantidad-promedio-por-día independientemente de la frecuencia de dosificación. Por ejemplo, una dosificación de 100 mg de un inhibidor de MK-2 tomada una vez cada dos días se expresaría como una frecuencia de dosificación de 50 mg/día. Análogamente, la frecuencia de dosificación de un ingrediente donde 50 mg se toman dos veces por día se expresaría como una frecuencia de dosificación de 100 mg/día.

[00081] Para efectos del cálculo de las cantidades posológicas, se asumirá que el peso de un humano adulto normal es 70 kg.

[00082] Cuando se administra un inhibidor de MK-2 junto con un vehículo farmacéuticamente aceptable, pueden formarse las composiciones farmacéuticas que se describen más arriba. Los vehículos farmacéuticamente aceptables incluyen, pero no se limitan a, solución salina fisiológica, solución de Ringer, solución de fosfato o amortiguadora, solución salina tamponada (***"buffered saline"***), y otros vehículos conocidos en el arte.

Las composiciones farmacéuticas pueden incluir asimismo estabilizantes, anti-oxidantes, colorantes, y diluyentes. Vehículos farmacéuticamente aceptables y aditivos se eligen de tal modo que se reduzcan al mínimo los efectos colaterales del compuesto farmacéutico y el rendimiento del compuesto no se cancele o inhiba en tal medida que el tratamiento sea ineficaz.

[00083] El término "cantidad farmacológicamente efectiva" significará que la cantidad de un medicamento o agente farmacéutica que producirá la respuesta médica o biológica de un tejido, sistema, animal o humano que se está buscando por el investigador o especialista clínico. Esta cantidad

puede ser una cantidad terapéuticamente efectiva.

[00084] El término "farmacéuticamente aceptable" se usa aquí para significar que el nombre modificado es apropiado para uso en un producto farmacéutico. Los cationes farmacéuticamente aceptables incluyen iones metálicos e iones orgánicos. Iones metálicos más preferidos incluyen, pero no se limitan a, sales apropiadas de metal alcalino, sales de metal alcalinotérreos y otros iones metálicos fisiológicos aceptables. Iones ejemplares incluyen aluminio, calcio, litio, magnesio, potasio, sodio y zinc en sus valencias usuales. Iones orgánicos preferidos incluyen aminas terciarias protonadas y cationes de amonio cuaternario, incluidos en parte, trimetilamina, dietilamina, N,N'-dibenciletilenediamina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumina (*N*-metilglucamina) y procaína. Acidos ejemplares farmacéuticamente aceptables incluyen, sin limitación, ácido clorhídrico, ácido yodhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico, ácido metanosulfónico, ácido acético, ácido fórmico, ácido tartárico, ácido maleico, ácido málico, ácido cítrico, ácido isocítrico, ácido succínico, ácido láctico, ácido glucónico, ácido glucurónico, ácido pirúvico, ácido oxalacético, ácido fumárico, ácido propiónico, ácido aspártico, ácido glutámico, ácido benzoico, y similares.

[00085] Asimismo se incluyen en los compuestos y composiciones de la invención las formas isoméricas y tautómeros y las sales farmacéuticamente aceptables de los presentes inhibidores de MK-2. Sales ilustrativas farmacéuticamente aceptables se preparan de ácidos fórmico, acético, propiónico, succínico, glicólico, glucónico, lactico, málico, tartárico, cítrico, ascórbico, glucurónico, maleico, fumárico, pirúvico, aspártico, glutámico, benzoico, antranílico, mesílico, esteárico, salicílico, p-hidroxibenzoico, fenilacético, mandélico, embónico (pamoico), metanosulfónico, etanosulfónico, bencenoesulfónico, pantoténico, toluenosulfónico, 2-hidroxietanosulfónico, sulfanílico, ciclohexilaminosulfónico, algénico, β-hidroxibutírico, galactárico y galacturónicos.

[00086] Sales de adición de ácido, farmacéuticamente aceptables, de

compuestos de la presente invención incluyen sales de iones metálicos y sales de iones orgánicos. Sales de iones metálicos más preferidos incluyen, pero no se limitan a, sales apropiadas de metal alcalino (Grupo IA), sales de metal alcalinotérreo (Grupo II A) y otros iones de metal, fisiológicos aceptables. Tales sales pueden prepararse de iones de aluminio, calcio, litio, magnesio, potasio, sodio y zinc. Sales orgánicas preferidas pueden elaborarse de aminas terciarias y sales de amonio cuaternario, incluidos en parte, trifluoroacetato, trimetilamina, dietilamina, *N,N'*-dibenciletilenediamina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumina (*N*-metilglucamina) y procaína. La totalidad de las sales ya mencionadas pueden prepararse por los expertos en el arte por métodos convencionales del compuesto correspondiente de la presente invención.

[00087] El método de la presente invención es útil para, pero no se limita a, la prevención y/o tratamiento de enfermedades y trastornos mediados por TNFα y/o mediados por MK-2, incluidos dolor, inflamación y/o artritis. Por ejemplo, los compuestos descritos aquí serían útiles para el tratamiento de cualquier trastorno relacionado con inflamación descrito a continuación, tal como un analgésico en el tratamiento de dolores y cefaleas, o como antipirético para el tratamiento de fiebre. Los compuestos descritos aquí serían asimismo útiles para el tratamiento de un trastorno relacionado con inflamación en un individuo que padece de tal trastorno asociado con inflamación.

[00088] Tal como se emplea aquí, los términos "tratando", "tratamiento", "tratado", o "tratar" significan aliviar los síntomas, eliminar la causa sobre una base permanente o temporal. El término "tratamiento" incluye alivio, eliminación de la causa del pain y/o inflamación asociados con, pero sin limitarse a, cualquiera de las enfermedades o trastornos descritos aquí. Los términos "previniendo", "prevención", "prevenido", o "prevenir," significan impedir o retardar la aparición de síntomas asociados con, pero sin limitarse a, cualquiera de las enfermedades o trastornos descritos aquí.

[00089] En incorporaciones preferidas, los métodos y composiciones de la presente invención abarcan la prevención y/o tratamiento de dolor,

inflamación y trastornos relacionados con inflamación.

[00090] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención comprenden el tratamiento de uno cualquiera o más de los trastornos seleccionados del grupo conformado por trastornos de las articulaciones y el tejido conectivo, trastornos de neoplasia, trastornos cardiovasculares, trastornos óticos, trastornos oftámicos, trastornos respiratorios, trastornos gastrointestinales, trastornos relacionados con angiogénesis, trastornos inmunitarios, trastornos alérgicos, trastornos de la nutrición, enfermedades y trastornos infecciosos, trastornos endocrinos, trastornos metabólicos, trastornos neurales y neurodegenerativos, trastornos psiquiátricos, trastornos hepáticos y biliares, trastornos del esqueleto mucular, trastornos genitourinarios, trastornos ginecológicos y obstétricos, trastornos ocasionados por lesiones y traumas, trastornos quirúrgicos, trastornos dentales y orales, trastornos de disfunción sexual, trastornos cutáneos, trastornos sanguíneos, y trastornos por envenenamiento.

[00091] Tal como se emplea aquí, los términos "neoplasia" y "trastorno de neoplasia", usados aquí en forma intercambiable, se refieren al crecimiento de nuevas células que resulta de la pérdida del grado de reacción a controles normales del crecimiento, *por ejemplo*, al crecimiento "neoplásico" de células. Neoplasia se usa también aquí en forma intercambiable con el término "cáncer" y para los propósitos de la presente invención; el cáncer es un subtipo de neoplasia. Tal como se emplea aquí, el término "trastorno de neoplasia" comprende igualmente otras anomalías celulares, tales como hiperplasia, metaplasia y displasia. Los términos neoplasia, metaplasia, displasia e hiperplasia pueden emplearse aquí en forma intercambiable y se refieren generalmente a células que experimentan un crecimiento celular anormal.

[00092] Ambos términos, "neoplasia" y "trastorno de neoplasia", se refieren a un "neoplasma" o tumor, que pueden ser benignos, premalignos, metastásicos, o malignos. La presente invención comprende además neoplasias benignas, premalignas, metastásicas, o malignas. De igual manera la presente invención abarca tumores benignos, premalignos,

metastásicos, o malignos. Por consiguiente, la totalidad de las neoplasias o tumores benignos, premalignos, metastásicos, o malignos queda abarcada por la presente invención y pueden designarse en forma intercambiable, como neoplasia, neoplasmas o trastornos relacionados con neoplasia. En el arte los tumores se conocen generalmente por ser una masa de neoplasia o células "neoplásicas". Aunque para los propósitos de la presente invención hay que entender que incluso una célula neoplásica se considera un neoplasma o, alternativamente, neoplasia.

[00093] En otras incorporaciones aún preferidas, los métodos y composiciones de la presente invención abarcan la prevención y tratamiento de trastornos de las articulaciones y el tejido conectivo seleccionados del grupo conformado por artritis, artritis reumatoide, espondiloartopatías, artritis gotosa, espondiloartrosis lumbar, síndrome del túnel carpiano, displasia de cadera en caninos, lupus sistémico eritematoso, artritis de los jóvenes, osteoartritis, tendinitis y bursitis.

[00094] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención incluyen la prevención y tratamiento de los trastornos de neoplasia seleccionados del grupo conformado por melanoma lentiginoso acral, queratosis actínicas, adenocarcinoma, carcinoma quístico adenoide, adenomas, poliposis adenomatosa familiar, pólipos familiares, pólipos de colon, pólipos, adenosarcoma, carcinoma adenoescamoso, carcinoma adrenocortical, linfoma relacionado con SIDA, cáncer anal, tumores astrocíticos, carcinoma de la glándula de Bartolino, carcinoma de las células basales, cáncer de los conductos biliares, cáncer de vejiga, glioma del tronco encefálico, tumores cerebrales, cáncer de mama, carcinomas de la glándula bronquial, carcinoma capilar, carcinoides, carcinoma, carcinosarcoma, cavernoso, linfoma del sistema nervioso central, astrocitoma cerebral, colangiocarcinoma, condosarcoma, papiloma/carcinoma choriod plexusdel plexo corioide, carcinoma de las células claras, cáncer cutáneo, cáncer cerebral, cáncer del colon, cáncer colorrectal, linfoma de células T cutáneas, cistadenoma, tumor de los senos endodérmicos, hiperplasia endometrial, sarcoma de estroma endometrial,

adenocarcinoma endometrioide, cáncer ependimal, epiteloide, esofágico, sarcoma de Ewing, tumor de células germinativas extragonadales, hiperplasia fibrolaminar, hiperplasia nodular focal, cáncer de la vesícula biliar, gastrinoma, tumores de las células germinativas, tumor trofoblástico del embarazo, gliobiastoma, glioma, glucagonoma, hemangioblastomas, hemangioendotelioma, hemangiomas, adenoma hepático, adenomatosis hepática, carcinoma hepatocelular, linfoma de Hodgkin, cáncer hipofaríngeo, glioma de las vías visuales y del hipotálamo, insulinoma, neoplasia intraepitelial, neoplasia escamosa interepitelial, melanomaintra ocular, carcinoma escamoso invasivo, carcinoma de células grandes, carcinoma de las células del islote, sarcoma de Kaposi, cáncer renal, cáncer de laringe, leiomiosarcoma, melanomas de lentigo maligna, trastornos relacionados con leucemia, cáncer de los labios y la cavidad oral, cáncer hepático, cáncer pulmonar, linfoma, tumores mesoteliales malignos, timoma maligno, méduloblastoma, méduloepitelioma, melanoma, carcinoma de las meninges, carcinoma de las células de Merkel, mesotelial, metastásico, carcinoma mucoepidermoide, neoplama de las células del plasma/mieloma múltiple, micosis fungoides, síndrome mielodisplásico, trastornos mieloproliferativos, cáncer de los senos paranasales y la cavidad nasal, cáncer nasofaríngeo, neuroblastoma, adenocarcinoma neuroepitelial, melanoma nodular, linfoma no hodgkiniano, carcinoma de células en avena (*"oat cell carcinoma"*), oligodendroglial, cáncer bucal, cáncer bucofaríngeo, osteosarcoma, polipéptido pancreático, cáncer ovárico, tumor de las células germinativas ováricas, cáncer pancreático, adenocarcinoma seroso papilar, tumores de células pineales, tumores de la pituitaria, plasmacitoma, pseudosarcoma, blastoma pulmonar, cáncer paratiroideo, cáncer del pene, feocromocitoma, tumores neuroectodérmicos primitivos pineales y supratentoriales, tumor de la pituitaria, neoplama de las células del plasma, blastoma pleuropulmonar, cáncer de próstata, cáncer rectal, carcinoma de las células renales, retinoblastoma, rabdomiosarcoma, sarcoma, carcinoma seroso, carcinoma microcítico, cáncer del intestino delgado, carcinomas de los tejidos blandos, tumor secretor de

somatostatina, carcinoma escamoso, carcinoma epidermoide (***"squamous cell carcinoma"***), mealonoma submesotelial, melanoma de propagación superficial, tumores neuroectodérmicos primitivos supratentoriales, cáncer de la tiroides, carcinoma no diferenciado, cáncer de la uretra, sarcoma uterina, melanoma de la úvea, carcinoma verrugoso, cáncer vaginal, vipoma, cáncer de la vulva, macroglobulinemia de Waldenstrom, carcinoma bien diferenciado, y tumor de Wilm.

[00095] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención comprenden la prevención y tratamiento de los trastornos cardiovasculares seleccionados del grupo conformado por isquemia del miocardio, hipertensión, hipotensión arterial, arritmias cardiacas, hipertensión pulmonar, hipocalemia, isquemia cardiaca, infarto del miocardio, remodelamiento cardiaco, fibrosis cardiaca, necrosis del miocardio, aneurisma, fibrosis arterial, embolismo, inflamación de las placas vasculares, ruptura de las placas vasculares, inflamación inducida por bacterias e inflamación inducida por virus, edema, hinchazón, acumulación de líquidos, cirrosis hepática, síndrome de Bartter, miocarditis, arterioesclerosis, ateroesclerosis, calcificación (tal como calcificación vascular y calcificación valvuvar), arteriopatía coronaria, insuficiencia cardiaca, insuficiencia cardiaca congestiva, choque, arritmia, hipertrofia ventricular izquierda, angina, nefropatía diabética, falla renal, daño ocular, vasculopatías, cefaleas con jaqueca, anemia aplásica, daño cardiaco, miopatía cardiaca diabética, insuficiencia renal, lesión renal, arteriopatía renal, vasculopatía periférica, hipertrofia ventricular izquierda, disfunción cognitiva, apoplejía, y cefalea.

[00096] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención incluyen la prevención y tratamiento de los trastornos metabólicos seleccionados del grupo conformado por obesidad, sobrepeso, diabetes tipo I y II, hipotiroidismo, e hipertiroidismo.

[00097] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención abarcan la prevención y tratamiento de los trastornos respiratorios seleccionados del grupo conformado por asma,

bronquitis, enfermedad pulmonar obstructiva crónica (COPD), fibrosis quística, edema pulmonar, embolismo pulmonar, neumonía, sarcoidosis, silicosis, fibrosis pulmonar, insuficiencia respiratoria, síndrome disneico agudo y enfisema.

[00098] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención incluyen la prevención y tratamiento de los trastornos relacionados con la angiogénesis seleccionados del grupo conformado por angiofibroma, glaucoma neovascular, anomalías arteriovenosas, artritis, síndrome de Osler-Weber, placas ateroescleróticas, psoriasis, neovascularización de injerto de córnea, granuloma pirogénico, cicatrización retrasada, fibroplasias retrolentales, retinopatía diabética, escleroderma, granulaciones, tumores sólidos, hemangioma, tracoma, articulaciones hemófilas, adhesiones vasculares, cicatrices hipertróficas, degeneración macular relacionada con la edad, arteriopatía coronaria, apoplejía, cáncer, complicaciones del SIDA, úlceras e infertilidad.

[00099] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención abarcan la prevención y tratamiento de las enfermedades y trastornos infecciosos seleccionados del grupo conformado por infecciones víricas, infecciones bacterianas, infecciones por priones, infecciones por espiroquetas, infecciones micobacterianas, rickettiosis, infecciones por clamidia, infecciones parasitarias e infecciones fúngicas.

[000100] En todavía otras incorporaciones, los métodos y composiciones de la presente invención comprenden la prevención y tratamiento de las enfermedades y trastornos infecciosos seleccionados del grupo conformado por hepatitis, VIH (SIDA), viruela, varicela, resfriado común, gripe bacteriana, gripe vírica, verrugas, herpes bucal, herpes genital, infecciones por herpes simplex, herpes zoster, encefalopatía espongiforme bobina, septicemia, infecciones por estreptococo, infecciones por estafilolococos, ántrax, síndrome respiratorio agudo y grave (SARS), malaria, enfermedad africana del sueño, fiebre amarilla, clamidia, botulismo, gusano del corazón en perros, fiebre de las montañas rocosas (***"rocky mountain spotted fever"***), enfermedad de Lyme, cólera, sífilis,

gonorrea, encefalitis, neumonía, conjuntivitis, candidiasis, rabia, fiebre del dengue, ebola, sarampión, paperas, rubéola, virus del Nilo Occidental, meningitis, gastroenteritis, tuberculosis, hepatitis, y escarlatina.

[000101] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención comprenden la prevención y tratamiento de los trastornos neuronales y neurodegenerativos seleccionados del grupo conformado por cefaleas, cefaleas con migraña, enfermedad de Alzheimer, enfermedad de Parkinson, demencia, pérdida de la memoria, senilidad, amiotrofia, ALS, amnesia, convulsiones, esclerosis múltiple, distrofias musculares, epilepsia, esquizofrenia, depresión, ansiedad, trastorno de falta de atención, hiperactividad, bulimia, anorexia nervosa, ansiedad, autismo, fobias, encefalopatías espongiformes, enfermedad de Creutzfeldt-Jakob, corea de Huntington, isquemia, trastorno obsesivo-compulsivo, depresión maníaca, trastornos bipolares, adicción a las drogas, alcoholismo y adicción al cigarrilo.

[000102] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención abarcan la prevención y tratamiento de los trastornos cutáneos seleccionados del grupo conformado por acné, psoriasis, eczema, quemaduras, hiedra venenosa, roble venenoso y dermatitis.

[000103] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención incluyen la prevención y tratamiento de los trastornos quirúrgicos seleccionados del grupo conformado por dolor e hinchazón pos-quirúrgicos, infección pos-quirúrgica e inflamación pos-quirúrgica.

[000104] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención abarcan la prevención y tratamiento de los trastornos gastrointestinales seleccionados del grupo conformado por enfermedad inflamatoria intestinal, síndrome de intestino irritable, enfermedad de Crohn, gastritis, síndrome del intestino irritable, diarrea, estreñimiento, disentería, colitis ulcerosa, reflujo gástrico esofágico, úlceras gástricas, varices gástricas, úlceras, y acidez gástrica.

[000105] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención incluyen la prevención y tratamiento de los trastornos óticos seleccionados del grupo conformado por dolor ótico, inflamación, otorrea, otalgia, fiebre, sangrado ótico, síndrome de Lermoyez, enfermedad de Meniere, neuronitis vestibular, vértigo posicional paroxísmico benigno, herpes zoster oticus, síndrome de Ramsay Hunt, neuronitis vírica, ganglionitis, herpes geniculado, labirintitis, labirintitis purulenta, labirintitis endolinfática vírica, fístulas perilinfáticas, pérdida de la audición inducida por ruido, deficiencia auditiva por vejez, ototoxicidad inducida por fármacos, neuromas acústicos, aerotitis media, inflamación infecciosa del tímpano, miringitis con vesículas, otitis media, otitis media con efusión, otitis media aguda, otitis media secretora, otitis media serosa, mastoiditis aguda, otitis media crónica, otitis externa, otoesclerosis, carcinoma escamoso, carcinoma basocelular, paragangliomas no cromafines, quimiodectomas, tumores del globus jugulare, tumores del globus tympanicum, otitis externa, pericondritis, dermatitis eczematoide auricular, otitis externa maligna, hematoma subpericondrial, ceruminomas, cerumen taponado, quistes sebáceos, osteomas, queloides, otalgia, zumbido en los oídos, vértigo, infección de la membrana timpánica, timpanitis, furúnculos óticos, otorrea, mastoiditis aguda, petrositis, pérdida de la audición conductiva y sensorineural, abceso epidural, trombosis de los senos laterales, empiema subdural, hidrocefalia otítica, síndrome de Dandy, miringitis con vesículas, cerumen taponado, otitis externa difusa, cuerpos extraños, keratosis obturans, neoplasma ótico, otomicosis, trauma, barotitis media aguda, obstrucción aguda de la tuba auditiva, cirugía pos-ótica, otalgia pos-quirúrgica, colesteatoma, pérdida de la audición conductiva y sensorineural, abceso epidural, trombosis de los senos laterales, empiema subdural e hidrocefalia otítica.

[000106] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención abarcan la prevención y tratamiento de los trastornos oftálmicos seleccionados del grupo conformado por retinopatías, uveítis, fotofobia ocular, lesión aguda al tejido ocular,

conjuntivitis, retinopatía diabética por degeneración macular relacionada con la edad, retina desprendida, glaucoma, distrofia macular viteliforme tipo 2, atrofia gyrata de la coroide y la retina, conjuntivitis, infección de la córnea, distrofia de Fuchs, síndrome endotelial iridocorneal, queratocono, distrofia en empalizada (***"lattice dystrophy"***), distrofia corneal en mapa-punto-huella (***"map-dot-fingerprint dystrophy"***), herpes ocular, pterigio, miopía, hiperopía, y cataratas.

[000107] En otras incorporaciones preferidas, los métodos y composiciones de la presente invención contienen la prevención y tratamiento de cólicos menstruales, cálculos biliares, lesiones menores, cicatrización de heridas, vaginitis, candidiasis, cefaleas de los senos, cefaleas por tensión, dolor dental, periarteritis nodosa, tiroiditis, myasthenia gravis, esclerosis múltiple, sarcoidosis, síndrome nefrótico, síndrome Behcet, polimiositis, gingivitis, hipersensibilidad, hinchazón después de una lesión, lesión cerebral cerrada (***"closed head injury"***), enfermedad hepática, y endometriosis.

[000108] Tal como se emplea aquí, el términos "enfermedad o trastorno mediado por TNFα" tienen como fin incluir, sin limitación, cada uno de los síntomas o enfermedades que se acaban de mencionar.

[000109] El término "individuo" para fines de tratamiento incluye cualquier individuo humano o animal que está necesitado de la prevención o tratamiento de una cualquiera de las enfermedades o trastornos mediados por TNFα. El individuo es típicamente un mamífero. "Mamífero", tal como ese término se emplea aquí, se refiere a cualquier animal clasificado como un mamífero, incluidos animales humanos, domésticos y de granja, animales de zoológico, animales deportivos, o mascotas, tales como perros, caballos, gatos, ganado, etc. Preferiblemente, el mamífero es un humano.

[000110] Para métodos de prevención, el individuo es cualquier individuo animal o humano, y preferiblemente es un individuo que se encuentra necesitado de prevención y/o tratamiento de enfermedades o trastornos mediados por TNFα. El individuo puede ser un individuo humano que está en riesgo de contraer una enfermedad o trastorno mediado

por TNFα, tal como los ya descritos. El individuo puede estar en riesgo debido a predisposición genética, estilo de vida sedentario, dieta, exposición a agentes causantes de trastornos, exposición a agentes patógenos y similares.

[000111] Las composiciones farmacéuticas en cuestión pueden administrarse enteral y parenteralmente. La administración parenteral incluye métodos subcutáneos, intramusculares, intradérmicos, intramamarios, intravenosos, y otros métodos administrativos conocidos en el arte. La administración enteral incluye soluciones, tabletas, cápsulas de liberación sostenida, cápsulas recubiertas entéricamente y jarabes. Cuando se administra, la composición farmacéutica puede estar a la temperatura corporal o cerca de ella.

[000112] En particular, las composiciones farmacéuticas de la presente invención pueden administrarse oralmente, por ejemplo, como tabletas, tabletas recubiertas, grageas, comprimidos medicinales, pastillas para chupar, suspensiones acuosas u oleosas, polvos o gránulos dispersables, emulsiones, cápsulas duras o blandas, o jarabes y elíxires. Las composiciones previstas para empleo oral pueden prepararse de acuerdo con cualquier método conocido en el arte para la manufactura de composiciones farmacéuticas y tales composiciones pueden contener uno o más agentes seleccionados del grupo conformado por agentes edulcorantes, agentes saborizantes, agentes colorantes y agentes preservantes, con el fin de ofrecer preparaciones farmacéuticamente elegantes y agradables. Las tabletas contienen el ingrediente activo en mezcla con excipientes farmacéuticamente aceptables, atóxicos, que son apropiados para la manufactura de tabletas. Estos excipientes pueden ser, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes o desagregantes, por ejemplo, almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo almidón, gelatina o acacia, y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Las tabletas pueden no recubrirse o pueden recubrirse por técnicas conocidas para

retrasar la desagregación y adsorción en el tubo digestivo y proveen así una acción sostenida durante un período más prolongado. Por ejemplo, puede emplearse un material de retraso del tiempo tal como monoestearato de glicerilo y diestearato de glicerilo.

[000113] Las formulaciones para uso oral pueden presentarse asimismo como cápsulas duras de gelatina en donde los ingredientes activos se mezclan con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas blandas de gelatina en donde los ingredientes activos están presentes como tales, o mezclados con agua o un medio oleoso, por ejemplo, aceite de maní, parafina líquida, o aceite de oliva.

[000114] Pueden producirse suspensiones acuosas que contengan los inhibidores de MK-2 en mezcla con excipientes apropiados para la manufactura de suspensiones acuosas. Tales excipientes son agentes de suspensión, por ejemplo, carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes pueden ser fosfátidos de ocurrencia en la naturaleza, por ejemplo lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo estearato de polioxietileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietileno y sorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de polioxietileno y sorbitán.

[000115] Las suspensiones acuosas pueden contener igualmente uno o más preservantes, por ejemplo, etil o n-propil p-hidroxibenzoato, uno o más agentes colorantes, uno o más agentes saborizantes, o uno o más agentes edulcorantes, tales como sacarosa o.

[000116] Pueden formularse suspensiones oleosas suspendiendo los ingredientes activos en un ácido graso omega-3, un aceite vegetal, por

ejemplo aceite de cacahuete, aceite de oliva, aceite de ajonjolí o aceite de coco, o en un aceite mineral tal como parafina líquida. Las suspensiones oleosas pueden contener un agente espesante, por ejemplo cera de abejas, parafina dura o alcohol cetílico.

[000117] Pueden agregarse agentes edulcorantes, tales como los expuestos anteriormente, y agentes saborizantes para ofrecer una preparación oral agradable. Estas composiciones pueden preservarse mediante la adición de un antioxidante tal como ácido ascórbico.

[000118] Agentes y gránulos dispersables apropiados para la preparación de una suspensión acuosa mediante la adición de agua proporcionan el ingrediente activo en mezcla con un agente dispersante o humectante, un agente de suspensión y uno o más preservantes. Agentes dispersantes o humectantes adecuados y agentes de suspensión se ejemplifican por aquellos ya mencionados más arriba en el texto. De la misma forma pueden estar presentes otros excipientes, por ejemplo agentes edulcorantes, saborizantes y colorantes.

[000119] jarabes y elíxires que contengan los novedosos compuestos inhibidores de MK-2 pueden formularse con agentes edulcorantes, por ejemplo glicerol, sorbitol o sacarosa. Tales formulaciones pueden contener además agentes suavizantes, preservantes, saborizantes y colorantes.

[000120] Las composiciones en cuestión pueden administrarse también por vía parenteral, ya sea subcutánea, o intravenosa, o intramuscular, o intrasternal, o mediante técnicas de infusión, en la forma de suspensiones acuosas o colagenosas inyectables estériles. Tales suspensiones pueden formularse de acuerdo con el arte conocido usando aquellos agentes dispersantes o humectantes y de suspensión apropiados, que se han mencionado más arriba u otros agentes aceptables. La preparación inyectable estéril puede ser asimismo una solución o suspensión inyectable estéril en un diluyente o disolvente parenteralmente aceptable, atóxico, por ejemplo como una solución 1,3-butanodiol. Entre los vehículos y disolventes aceptables que pueden emplearse se encuentran agua, solución de Ringer y solución de cloruro de sodio isotónico. Además, aceites fijos

estériles se emplean convencionalmente como disolvente o medio de suspensión. Para este propósito, puede empelarse cualquier aceite fijo suave, inclusive mono-, o di-glicéridos sintéticos. Adicionalmente, ácidos grasos poliinsaturados n-3 pueden encontrar aplicación en la preparación de inyectables.

[000121] Las composiciones en cuestión pueden administrarse también por inhalación, en la forma de aerosoles o soluciones para nebulizadores, o por vía rectal, en la forma de supositorios preparados mezclando el medicamento con un excipiente no irritante apropiado, que es sólido a la temperatura ordinaria pero líquido a la temperatura del recto y que, por lo tanto, se derretirá en el recto para liberar el medicamento. Tales materiales son manteca de cacao y polietilen glicoles.

[000122] Las novedosas composiciones pueden administrarse asimismo localmente, en la forma de cremas, ungüentos, geles, colirios, soluciones o suspensiones.

[000123] Varios sistemas de administración incluyen cápsulas, tabletas, y cápsulas de gelatina, por ejemplo.

[000124] Los siguientes ejemplos describen incorporaciones preferidas de la invención. Otras incorporaciones dentro del ámbito de las reivindicaciones contenidas aquí serán evidentes a un experto en el arte a partir de la consideración de la especificación o práctica de la invención como se divulga aquí. Se pretende que la especificación, junto con los Ejemplos, se considere ejemplar únicamente, indicándose el ámbito y el espíritu de la invención por las reivindicaciones que siguen a los Ejemplos. En los Ejemplos todos los porcentajes están dados en una base de peso, a menos que se indique lo contrario.

INFORMACIÓN GENERAL DE LOS MÉTODOS DE PREPARACIÓN:

[000125] Salvo que se anote otra cosa, los reactivos y disolventes se utilizaron tal como se recibieron de los proveedores comerciales.

[000126] Análisis de NMR:

[000127] Se obtuvieron espectros de resonancia magnética nuclear de

protones en un espectrómetro Varian Unity Innova 400, Varian Unity Innova 300, Varian Unity 300, Bruker AMX 500 ó Bruker AV-300. Las variaciones químicas se dan en ppm (δ) y las constantes de acoplamiento, *J*, se reportan en Hertz. Se usó tetrametilsilano como estándar interno para los espectros de protones y el pico del disolvente se empleó como el pico de referencia para los espectros de carbono. Los espectros de masas se obtuvieron en un espectrómetro de masas con ionización de presión atmosférica (APCI) Perkin Elmer Sciex 100, un espectrómetro de masas con ionización de electroaspersión (ESI) de trampa de iones LCMS Finnigan LCQ Duo, un PerSeptive Biosystems Mariner TOF HPLC-MS (ESI), o un espectrómetro de masas (ESI) Waters ZQ.

[000128] Determinación de IC_{50} MK-2:

[000129] MAPKAPK2 recombinante se fosforiló con una concentración de 42-78 μM por incubación con 0.23 μM de p38α activo en 50 mM HEPES, 0.1 mM EDTA, 10 mM acetato de magnesio, y 0.25 mM ATP, pH 7.5 durante 1 hora a 30°C.

[000130] La fosforilación del péptido HSP (KKKALSRQLSVAA) por MAPKAPK2 se midió usando un método de ensayo de captura con resina de intercambio de aniones. La reacción se llevó a cabo en 50 mM β-glicerolfosfato, 0.04 % BSA, 10 mM acetato de magnesio, 2% DMSO y 0.8 mM ditioteritol, pH 7.5 en la presencia del péptido HSP con 0.2 μCi [γ^{33}P]ATP y 0.03mM ATP. La reacción se inició con la adición de 15 nM MAPKAPK2 y se dejó incubar a 30° durante 30 minutos. La reacción se terminó y se retiró [γ^{33}P]ATP de la solución mediante la adición de 150 μl de resina de intercambio de iones AG 1X8 en 900 mM formiato de sodio pH 3.0. Se retiró una alícuota de 50 μl del volumen de cabeza de la mezcla de reacción atemperada y se agregó a una placa de 96 pozos, se agregó 150 μl de Microscint-40 (Packard) y se determinó la cantidad de péptido fosforilado. Se dejó asentar el Microscint en las placas durante 60 minutos antes del conteo.

[000131] Los compuestos se evalúan como inhibidores potenciales de la cinasa MK2 midiendo sus efectos sobre la fosforilación de MK2 del

sustrato del péptido. Los compuestos pueden cribarse inicialmente con dos concentraciones antes de la determinación de los valores IC_{50}. Los resultados del cribado se expresan como inhibición porcentual con las concentraciones del compuesto probado. Para las determinaciones del valor IC_{50}, los compuestos se ensayan con seis concentraciones en diluciones décuples probándose cada concentración en triplicado. Los resultados se expresan como valores IC_{50} en micromolar. El análisis se realiza con una concentración final de 2% DMSO.

[000132] Análisis de Liberación TNFα de Células U937

[000133] La estirpe celular monocitoide humana ("***the human monocyte-like cell line***") U937 (ATCC #CRL-1593.2), se cultiva en medio RPMI1640 con 10% suero fetal bobino inactivado por calor (GIBCO), glutamina y pen/strep a 37°C y 5% CO_2. La diferenciación de U937 respecto a las células monocíticas/pseudomacrófago ("***monocytic/macrophage-like cells*** ") se induce por la adición de forbol 12-miristato 13-acetato (Sigma) con una concentración final de 20 ng/ml a un cultivo de células U937 con -0.5 millones de células/ml y se incuba durante 24 horas. Las células se centrifugan, se lavan con PBS y se re-suspenden en medio fresco sin PMA y se incuban durante 24 horas. Se recogen por raspado las células adheridas al matraz de cultivo, centrifugación, y se re-suspenden en medio fresco a 2 millones de células/ml, y se llevan alícuotas de 0.2 ml a cada uno de los 96 pozos en una placa de fondo plano. En seguida se incuban las células durante 24 horas más para permitir la recuperación. El medio se retira de las células, y se agrega 0.1 ml de medio fresco por pozo. Se agrega a las células 0.05 ml de compuesto diluido en serie o vehículo de control (medio con DMSO). La concentración final de DMSO no excede el 1%. Después de 1 hora de incubación, se agrega 0.05 ml de 400ng/ml LPS (E Coli serotipo 0111:B4, Sigma) en medio para una concentración final de 100 ng/ml. Las células se incuban a 37°C durante 4 horas. Luego de 4 horas de incubación, se recogen los sobrenadantes y se analizan por ELISA para detectar la presencia de TNFα.

[000134] ELISA de TNFα de Células U937

[000135] Placas ELISA (NUNC-Immuno™ Plate Maxisorb™ Surface) se cubrieron con anticuerpo TNFα anti-humano IgG1 monoclonal desarrollada en ratón, purificado ("***purified mouse monoclonal IgG1 anti-human TNFα antibody***") (R&D Systems #MAB610; 1.25 ug/ml en bicarbonato de sodio pH 8.0, 0.1 ml/pozo) y se incubaron a 4°C. Se aspiró la solución recubridora el siguiente día y los pozos se bloquearon con 1 mg/ml de gelatina en PBS (plus 1x timerasol) durante 2 días a 4°C. Antes de usarlos, los pozos se lavaron 3x con solución amortiguadora de lavado (PBS con 0.05% Tween). Las muestras de medio cultivados se diluyeron en solución amortiguadora EIA (5 mg/ml γ-globulina bobina, 1 mg/ml gelatina, 1 ml/l Tween-20, 1 mg/ml timerasol en PBS), se agregaron a los pozos (0.1 ml/pozo) en triplicado y se dejaron incubar durante 1.5 horas a 37°C en una cámara humidificada. Las placas se lavaron de nuevo y 0.1 ml/pozo de una mezcla de anticuerpos policlonales TNFα anti-humano de sarrollado en conejo en solución amortiguadora EIA (1:400 dilución de Sigma #T8300, y 1:400 dilución de Calbiochem #654250) se agregó durante 1 hora a 37°C. Las placas se lavaron al igual que antes e IgG (H+L) anti-conejo desarrollado en cabra, conjugada con peroxidasa ("***peroxidase-conjugated goat anti-rabbit IgG (H+L) antibody***") (Jackson ImmunoResearch #111-035-144, 1 ug/ml en solución amortiguadora EIA, 0.1 ml/pozo) se agregó durante 45 minutos. Luego del lavado final, las placas se revelaron con solución ABTS-peroxidasa (Kirkegaard/Perry #50-66-01, 0.1 ml/pozo). Se midió la conversión enzimática de ABTS en un producto coloreado después de 5-30 minutos usando un espectrofotómetro SpectroMax 340 (Molecular Devices) a 405 nm. Se cuantificaron los niveles de TNF de una curva estándar de TNFα humano recombinante (R&D Systems #210-TA-010) usando un ajuste de parámetros cuadrático generado por software SoftMaxPRO. La sensibilidad de ELISA fue de aproximadamente 30 pg TNF/ml. Los valores IC_{50} de los compuestos se generaron usando un BioAssay Solver.

[000136] <u>Producción de TNFα inducida por Polisacárido (LPS)</u>

[000137] Se usaron ratas Lewis macho adultas de 225-250 gramos

(Harlan Sprague-Dawley). Se privó a las ratas de alimento 18 horas antes de la dosificación oral, y se les permitió el libre acceso al agua de principio a fin del experimento. Cada grupo de tratamiento constaba de 5 animales.

[000138] Los compuestos se prepararon como una suspensión en un vehículo compuesto de 0.5% metilcelulosa, 0.025% Tween-20 en PBS. Los compuestos o vehículo se administraron oralmente en un volumen de 1 ml usando una aguja de alimentación por sonda gástrica, calibre 18. LPS (E. coli serotipo 0111:B4, Lote #39H4103, Cat. # L-2630, Sigma) se administró 1-4 horas después por inyección en la vena del pene con una dosis de 1 mg/kg en 0.5 ml de solución salina estéril. Se tomaron muestras de sangre en tubos separadores de suero mediante punción cardiaca 1.5 horas después de la inyección de LPS, un punto de tiempo correspondiente a una producción máxima de TNFα. Después de la coagulación, se retiró suero y se almacenó a -20°C hasta el ensayo por ELISA (descrito más adelante).

[000139] ELISA TNFα LPS de Rata

[000140] Placas ELISA (NUNC-Immuno™ Plate Maxisorb™ Surface) se cubrieron con 0.1 ml por pozo de una fracción purificada de Proteina G de 2.5 ug/ml de anti-cuerpo monoclonal TNFα anti-ratón/rata de hámster TN19.12 (2.5 ug/ml en PBS, 0.1 ml/pozo). La estirpe celular del hibridoma fue gentilmente suministrada por el Dr. Robert Schreiber, Universidad de Washington. Los pozos se bloquearon el día siguiente con1 mg/ml gelatina en PBS. Las muestras de suero se diluyeron en una solución amortiguadora que constaba de 5 mg/ml de γ-globulina bobina, 1 mg/ml gelatina, 1 ml/l Tween-20, 1 mg/ml timerasol en PBS, y 0.1 ml de suero diluido se agregaron a los pozos en duplicado y se dejaron incubar durante 2 horas a 37°C. Las placas se lavaron con PBS-Tween, y 0.1 ml por pozo de una dilución 1:300 de anticuerpo TNFα anti-ratón/rata desarrollada en conejo (BioSource International, Cat. #AMC3012) se agregó durante 1.5 horas a 37°C. Las placas se lavaron, y una dilución 1:1000 de anti-cuerpo IgG anti-conejo desarrollado en asno, conjugado con peroxidasa (Jackson ImmunoResearch, Cat. #711-035-152) se agregó durante 45 minutos. Luego de lavar, las placas se revelaron con 0.1 ml de solución de ABTS-

peróxido (Kirkegaard/Perry, Cat. #50-66-01). La conversión enzimática de ABTS en un producto coloreado se midió después de ~30 minutos usando un espectrofotómetro SpectroMax 340 (Molecular Devices Corp.) a 405 nm. Los niveles de TNF en el suero se cuantificaron a partir de una curva estándar (BioSource International, Cat. #PRC3014) TNFα de rata recombinante usando un ajuste de parámetros cuadrático generado por software SoftMaxPRO. La sensibilidad de ELISA fue de aproximadamente 30 pg TNF/ml. Los resultados se expresan en inhibición porcentual de la producción de TNFα comparada con la sangre recogida de los animales de control dosificados únicamente con vehículo.

[000141] Análisis de NMR:

[000142] Se obtuvieron espectros de resonancia magnética nuclear de protones en un espectrómetro Varian Unity Innova 400, Varian Unity Innova 300, Varian Unity 300, Bruker AMX 500 ó Bruker AV-300. Las variaciones químicas se dan en ppm (δ) y las constantes de acoplamiento, *J*, se reportan en Hertz. Se usó tetrametilsilano como estándar interno para los espectros de protones y el pico del disolvente se empleó como el pico de referencia para los espectros de carbono. Los espectros de masas se obtuvieron en un espectrómetro de masas con ionización de presión atmosférica (APCI) Perkin Elmer Sciex 100, un espectrómetro de masas con ionización de electroaspersión (ESI) de trampa de iones LCMS Finnigan LCQ Duo, un PerSeptive Biosystems Mariner TOF HPLC-MS (ESI), o un espectrómetro de masas (ESI) Waters ZQ.

[000143] Determinación de IC_{50} MK-2:

[000144] MAPKAPK2 recombinante se fosforiló con una concentración de 42-78 μM por incubación con 0.23 μM de p38α activo en 50 mM HEPES, 0.1 mM EDTA, 10 mM acetato de magnesio, y 0.25 mM ATP, pH 7.5 durante 1 hora a 30°C.

[000145] La fosforilación del péptido HSP (KKKALSRQLSVAA) por MAPKAPK2 se midió usando un método de ensayo de captura con resina de intercambio de aniones. La reacción se llevó a cabo en 50 mM β-glicerolfosfato, 0.04 % BSA, 10 mM acetato de magnesio, 2% DMSO y 0.8

mM ditioteritol, pH 7.5 en la presencia del péptido HSP con 0.2 μCi [γ^{33}P]ATP y 0.03mM ATP. La reacción se inició con la adición de 15 nM MAPKAPK2 y se dejó incubar a 30° durante 30 minutos. La reacción se terminó y se retiró [γ^{33}P]ATP de la solución mediante la adición de 150 μl de resina de intercambio de iones AG 1X8 en 900 mM formiato de sodio pH 3.0. Se retiró una alícuota de 50 μl del volumen de cabeza de la mezcla de reacción atemperada y se agregó a una placa de 96 pozos, se agregó 150 μl de Microscint-40 (Packard) y se determinó la cantidad de péptido fosforilado. Se dejó asentar el Microscint en las placas durante 60 minutos antes del conteo.

[000146] Los compuestos se evalúan como inhibidores potenciales de la cinasa MK2 midiendo sus efectos sobre la fosforilación de MK2 del sustrato del péptido. Los compuestos pueden cribarse inicialmente con dos concentraciones antes de la determinación de los valores IC_{50}. Los resultados del cribado se expresan como inhibición porcentual con las concentraciones del compuesto probado. Para las determinaciones del valor IC_{50}, los compuestos se ensayan con seis concentraciones en diluciones décuples probándose cada concentración en triplicado. Los resultados se expresan como valores IC_{50} en micromolar. El análisis se realiza con una concentración final de 2% DMSO.

[000147] Análisis de Liberación de TNFα de Células U937

[000148] La estirpe celular monocitoide humana, U937 (ATCC #CRL-1593.2), se cultiva en medio RPMI1640 con 10% suero fetal bobino inactivado por calor (GIBCO), glutamina y pen/strep a 37°C y 5% CO_2. La diferenciación de U937 respecto a las células monocíticas/pseudomacrófago se induce por la adición de forbol 12-miristato 13-acetato (Sigma) con una concentración final de 20 ng/ml a un cultivo de células U937 con ~0.5 millones de células/ml y se incuba durante 24 horas. Las células se centrifugan, se lavan con PBS y se re-suspenden en medio fresco sin PMA y se incuban durante 24 horas. Se recogen por raspado las células adheridas al matraz de cultivo, centrifugación, y se re-suspenden en medio fresco a 2 millones de células/ml, y se llevan alícuotas de 0.2 ml a cada uno de los 96

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pozos en una placa de fondo plano. En seguida se incuban las células durante 24 horas más para permitir la recuperación. El medio se retira de las células, y se agrega 0.1 ml de medio fresco por pozo. Se agrega a las células 0.05 ml de compuesto diluido en serie o vehículo de control (medio con DMSO). La concentración final de DMSO no excede el 1%. Después de 1 hora de incubación, se agrega 0.05 ml de 400ng/ml LPS (E Coli serotipo 0111:B4, Sigma) en medio para una concentración final de 100 ng/ml. Las células se incuban a 37°C durante 4 horas. Luego de 4 horas de incubación, se recogen los sobrenadantes y se analizan por ELISA para detectar la presencia de TNFα.

[000149] ELISA de TNFα de Células U937

[000150] Placas ELISA (NUNC-Immuno™ Plate Maxisorb™ Surface) se cubrieron con anticuerpo TNFα anti-humano IgG1 monoclonal desarrollado en ratón, purificado (R&D Systems #MAB610; 1.25 ug/ml en bicarbonato de sodio pH 8.0, 0.1 ml/pozo) y se incubaron a 4°C. Se aspiró la solución recubridora el siguiente día y los pozos se bloquearon con 1 mg/ml de gelatina en PBS (plus 1x timerasol) durante 2 días a 4°C. Antes de usarlos, los pozos se lavaron 3x con solución amortiguadora de lavado (PBS con 0.05% Tween). Las muestras de medio cultivadas se diluyeron en solución amortiguadora EIA (5 mg/ml γ-globulina bobina, 1 mg/ml gelatina, 1 ml/l Tween-20, 1 mg/ml timerasol en PBS), se agregaron a los pozos (0.1 ml/pozo) en triplicado y se dejaron incubar durante 1.5 horas a 37°C en una cámara humidificada. Las placas se lavaron de nuevo y 0.1 ml/pozo de una mezcla de anticuerpos policlonales TNFα anti-humano de conejo en solución amortiguadora EIA (1:400 dilución de Sigma #T8300, y 1:400 dilución de Calbiochem #654250) se agregó durante 1 hora a 37°C. Las placas se lavaron al igual que antes e IgG (H+L) anti-conejo desarrollado en cabra, conjugado con peroxidasa (Jackson ImmunoResearch #111-035-144, 1 ug/ml en solución amortiguadora EIA, 0.1 ml/pozo) se agregó durante 45 minutos. Luego del lavado final, las placas se revelaron con solución ABTS-peroxidasa (Kirkegaard/Perry #50-66-01, 0.1 ml/pozo). Se midió la conversión enzimática de ABTS en un producto coloreado

después de 5-30 minutos usando un espectrofotómetro SpectroMax 340 (Molecular Devices) a 405 nm. Se cuantificaron los niveles de TNF de una curva estándar de TNFα humano recombinante (R&D Systems #210-TA-010) usando un ajuste de parámetros cuadrático generado por software SoftMaxPRO. La sensibilidad de ELISA fue de aproximadamente 30 pg TNF/ml. Los valores IC_{50} de los compuestos se generaron usando un BioAssay Solver.

[000151] Producción de TNFα inducida por Lipopolisacárido (LPS).

[000152] Se usaron ratas Lewis macho adultas de 225-250 gramos (Harlan Sprague-Dawley). Se privó a las ratas de alimento 18 horas antes de la dosificación oral, y se les permitió el libre acceso al agua de principio a fin del experimento. Cada grupo de tratamiento constaba de 5 animales.

[000153] Los compuestos se prepararon como una suspensión en un vehículo compuesto de 0.5% metilcelulosa, 0.025% Tween-20 en PBS. Los compuestos o vehículo se administraron oralmente en un volumen de 1 ml usando una aguja de alimentación por sonda gástrica, calibre 18. LPS (E. coli serotipo 0111:B4, Lote #39H4103, Cat. # L-2630, Sigma) se administró 1-4 horas después por inyección en la vena del pene con una dosis de 1 mg/kg en 0.5 ml de solución salina estéril. Se tomaron muestras de sangre en tubos separadores de suero mediante punción cardiaca 1.5 horas después de la inyección de LPS, un punto de tiempo correspondiente a una producción máxima de TNFα. Después de la coagulación, se retiró suero y se almacenó a -20°C hasta el ensayo por ELISA (descrito más adelante).

[000154] ELISA de TNFα LPS de Rata

[000155] Placas ELISA (NUNC-Immuno™ Plate Maxisorb™ Surface) se cubrieron con 0.1 ml por pozo de una fracción purificada de Proteina G de 2.5 ug/ml de anti-cuerpo monoclonal TNFα anti-ratón/rata de hámster TN19.12 (2.5 ug/ml en PBS, 0.1 ml/pozo). La estirpe celular del hibridoma fue gentilmente suministrada por el Dr. Robert Schreiber, Universidad de Washington. Los pozos se bloquearon el día siguiente con1 mg/ml gelatina en PBS. Las muestras de suero se diluyeron en una solución amortiguadora que constaba de 5 mg/ml de γ-globulina bobina, 1 mg/ml gelatina, 1 ml/l

Tween-20, 1 mg/ml timerasol en PBS, y 0.1 ml de suero diluido se agregaron a los pozos en duplicado y se dejaron incubar durante 2 horas a 37°C. Las placas se lavaron con PBS-Tween, y 0.1 ml por pozo de una dilución 1:300 de anticuerpo TNFα anti-ratón/rata desarrollado en conejo (BioSource International, Cat. #AMC3012) se agregó durante 1.5 horas a 37°C. Las placas se lavaron, y una dilución 1:1000 de anti-cuerpo IgG anti-conejo desarrollado en asno, conjugado (Jackson ImmunoResearch, Cat. #711-035-152) se agregó durante 45 minutos. Luego de lavar, las placas se revelaron con 0.1 ml de solución de ABTS-peróxido (Kirkegaard/Perry, Cat. #50-66-01). La conversión enzimática de ABTS en un producto coloreado se midió después de ~30 minutos usando un espectrofotómetro SpectroMax 340 (Molecular Devices Corp.) a 405 nm. Los niveles de TNF en el suero se cuantificaron a partir de una curva estándar (BioSource International, Cat. #PRC3014) TNFα de rata recombinante usando un ajuste de parámetros cuadrático generado por software SoftMaxPRO. La sensibilidad de ELISA fue de aproximadamente 30 pg TNF/ml. Los resultados se expresan en inhibición porcentual de la producción de TNFα comparada con la sangre recogida de los animales de control dosificados únicamente con vehículo.

[000156] Síntesis de los Compuestos Inhibidores de MK-2 de la presente invención:

[000157] A menos que se anote otra cosa, los reactivos y solventes se usaron tal como se recibieron de los proveedores comerciales. Los espectros de resonancia magnética nuclear de protones se obtuvieron en un espectrómetro Varian-300, Bruker AMX 500 o Bruker AV-300. Los espectros se dan en ppm (δ) y las constantes de acoplamiento, *J*, se reportan en Hertz. Se usó tetrametilsilano como estándar interno para los espectros de protones y el pico del disolvente se usó como el pico de referencia para los espectros de carbono. Se empleó 3-bromobenzotrifluoruro como un estándar interno en espectros de resonancia magnética nuclear ^{19}F para calibrar la cantidad de TFA para sales TFA. Los espectros de masas de se btuvieron en ionización por electrodispersión

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(ESI) Mariner, espectrómetro de masas con ionización a presión atmosférica (APCI) Perkin Elmer Sciex 100, ionización con trampa de iones (ESI) LMCS Hewlett Packard G1947A, o una ionización por electrodispersión (ESI) con trampa de iones LCMS Finnigan LCQ Duo. Se llevó a cabo cromatografía de capa delgada (TLC) usando placas de gel de sílice Analtech y se visualizó por luz ultravioleta (UV). Los análisis HPLC se obtuvieron usando una YMC CombiScreen ODS-A (50 x 4.6 mm) con UV con detección de arreglo de diodos, usando TFA acuoso en acetonitrilo como el eluyente en una columna Hewlett Packard 1100, o Phenomenex C18 Luna (150 x 4.6 mm) con detección UV a 254 nm, usando TFA acuoso en acetonitrilo como el eluyente en un Varian Prostar. La purificación usando HPLC preparativa se realizó usando una columna Phenomenex C18 Luna (250 x 22 mm) con detección UV a 254 nm, usando TFA acuoso en acetonitrilo como el eluyente en un Varian Prostar, o usando una columna Waters Deltapack C 18 (47 x 300 mm) con detección UV a 254 nm, usando TFA acuoso en acetonitrilo como el eluyente en una Gilson. Todas las reacciones se llevaron a cabo bajo nitrógeno a menos que se especifique otra cosa.

EJEMPLO 1

[000158] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato.

[000159] Paso 1. La preparación de (1Z)-4-etoxi-3,4-dioxo-1-piridin-4-ilbut-1-en-1-olato de litio.

[000160] 4-Acetilpiridina (960.4 g, 7.93 moles) y oxilato de dietilo (1170.8 g, 8.08 moles) se disolvieron en 8 L tolueno en un reactor de 22 L. La reacción se enfrió a -78°C bajo N_2, y se agregó una solución 1 M de bis(trimetilsilil)amida de litio en THF (8.08 L, 8.08 moles) en una corriente de medio durante 45 minutos, manteniendo la temperatura cerca de 10°C. Cuando la adición se completó, la reacción se dejó calentar a la temperatura de la sala agitando simultáneamente durante 18 horas. La mezcla de reacción se filtró, y el sólido se lavó con tolueno seguido por éter dietílico.

El producto se secó por aire y se desecó para proporcionar 1562.5 g de la sal de litio del dicetoéster (87% rendimiento).

[000161] Paso 2. (1Z)-4-etoxi-3,4-dioxo-1-piridin-4-ilbut-1-en-1-olato de litio (1562.5 g, 6.88 moles) se puso en un reactor de 22 L y se suspendió en 7 L de etanol. La suspensión se calentó a 63°C bajo N_2 mezclando simultáneamente. Se retiró la camisa de calefacción, y la temperatura se estabilizó a alrededor de 63°C. A esta mezcla se agregó monoclorhidrato de hidrazina(476.3 g, 6.95). Después de unos pocos minutos se inició una lenta exotermia. Se aplicó un baño de hielo/agua cuando la reacción alcanzó 80°C. El baño de hielo se retiró, y la temperatura se mantuvo constante a 80°C. Se reinstaló la camisa de calefacción, y la reacción se mantuvo a 80.5°C (reflujo) durante una hora. La reacción se enfrió y se agitó a la temperatura de la sala durante 18 horas. La mezcla se filtró, y los sólidos se lavaron con etanol seguido por éter dietílico. El producto se secó por aire y se desecó para proporcionar 1365.6 g (91% rendimiento) del pirazol deseado como un sólido amarillento. LCMS mostró un pico único con m/z 218 (M+H). ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.61 (d, 2H), 7.83 (d, 2H), 7.44 (s, 1H), 4.31 (q, 2H), 1.30 (t, 3H).

[000162] Paso 3. A una solución enfriada (0°C) de etil 3-piridin-4-il-1H-pirazol-5-carboxilato (5.57 g, 25.6 mmol) en DMF anhidro (140 mL) se agregó *t*-butóxido de litio (1M in THF, 38.5 mL) gota a gota. Se agitó la reacción durante 30 minutos, luego se agregó gota a gota una solución de *terc*-butil 2-bromoetilcarbamato (8.62 g, 38.5 mmol) y yoduro de sodio (5.77 g, 38.5 mmol) en DMF anhidro (25 mL). La reacción se dejó agitar y calentar a la temperatura de la sala durante 20 horas. La reacción se vertió en agua y salmuera, se extrajo con acetato de etilo, se secó sobre $MgSO_4$, y se concentró en un sólido anaranjado. El sólido se enjuagó con éter dietílico para proporcionar un sólido blancuzco (5.49 g, 59.5% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.59 (d, 2H), 7.82 (d, 2H), 7.51 (s, 1H), 6.90 (t, 1H), 4.58 (t, 2H), 4.33 (q, 2H), 3.38-3.33 (m, 2H), 1.34 (t, 3H), 1.27 (s, 9H); HRMS calculado para (M + H) 361.1870, hallado 361.1890.

EJEMPLO 2

[000163] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-amino-etil)-3-piridin-4-il-1H-pirazol-5-carboxilato.

[000164] A un matraz cargado con etil 1-{2-[(terc-butoxicarbonil)amino] etil}-3-piridin-4-il-1H-pirazol-5-carboxilato (5.39 g, 15.0 mmol) se agregó 4N HCl/dioxano (20 mL). Después de 1 hora la mezcla de reacción se filtró y se enjuagó con éter dietílico para proporcionar un sólido blancuzco (5.02 g, 100% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.93 (d, 2H), 8.48-8.43 (m, 5H), 7.95 (s, 1H), 4.89 (t, 2H), 4.37 (q, 2H), 3.41-.3.38 (m, 2H), 1.35 (t, 3H); HRMS calculado para (M + H) 261.1346, hallado 261.1317.

EJEMPLO 3

[000165] Este ejemplo ilustra la producción de trifluoroacetato de 2-piridin-4-il-6,7-dihidro-pirazolo[1,5-a]pirazin-4(5H)-ona.

[000166] Se cargó un matraz con diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1 H-pirazol-5-carboxilato (1.13 g, 3.39 mmol), NH_4OH (30 mL), y etanol (15 mL). Después de agitar durante 1 hora, la mezcla de reacción se purificó por Gilson RP HPLC (5-95% acetonitrilo/agua). Las fracciones apropiadas se concentraron en un sólido amarillo pálido (0.725 g, 65.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.81 (d, 2H), 8.40 (br s, 1H), 8.22 (d, 2H), 7.67 (s, 1H), 4.43 (t, 2H), 3.70-3.64 (m, 2H); HRMS calculado para (M + H) 215.0927, hallado 215.0885.

EJEMPLO 4

[000167] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico.

[000168] Una solución de diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato (0.794 g, 2.38 mmol) y $LiOH•H_2O$ (0.310 g, 7.40 mmol) en 30 mL de THF/H_2O (1:1) se calentó a 80°C agitando simultáneamente. Después de 2 horas la mezcla de reacción se purificó por

Gilson RP HPLC (5-95% acetonitrilo/agua). Las fracciones apropiadas se concentraron en un sólido blanco (0.442 g, 53.7% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.96 (br s, 2H), 8.48 (br s, 2H), 8.07-7.91 (m, 4H), 4.87 (brs, 2H), 3.41 (brs, 2H); HRMS calculado para (M + H) 233.1033, hallado 233.1025.

EJEMPLO 5

[000169] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(2-{[3-(5-metil-2-furil)butil]amino}etil)-3-piridin-4-il-1H-pirazol-5-carboxílico.

[000170] Diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato (0.806 g, 2.42 mmol) se neutralizó agitando con resina de morfolino-metilpoliestireno (4.15 g, ~3.5 mmol base/g resina) en diclorometano/metanol (20:1) durante 1 hora. La resina se filtró, se enjuagó con metanol, y los filtrados se concentraron. El residuo blanco resultante se disolvió en diclorometano/metanol (20:1). Se agregaron seis gotas de ácido acético glacial agitando simultáneamente, seguido por 3-(5-metil-2-furil)butiraldehído (0.422 g, 6.60 mmol. Después de 5 minutos, se agregó triacetoxiborohidruro de sodio (1.04 g, 4.90 mmol). La reacción se agitó durante 1 hora, y se formaron los dos productos mono- y dialquilados. La reacción se atemperó con agua y se extrajo con diclorometano. Las capas orgánicas se concentraron en un aceite, el cual se sometió a condiciones de hidrólisis [3 eq LiOH•H_2O, THF/H_2O (1:1)] durante 3 horas. La mezcla de producto resultante se purificó por Gilson RP HPLC (5-95% acetonitrilo/agua) y las fracciones correspondientes al producto monoalquilado se concentraron en un sólido color lila (0.106 g, 9.0% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.77-8.75 (m, 4H), 8.08 (d, 2H), 7.72 (s, 1H), 5.97-5.93 (m, 2H), 4.87 (t, 2H), 3.51-3.47 (m, 2H), 2.96 (brs, 2H), 2.82 (q, 1H), 2.19 (s, 3H), 1.92-1.72 (m, 2H), 1.16 (d, 3H); HRMS calculado para (M + H) 233.1033, hallado 233.1025.

EJEMPLO 6

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[000171] Este ejemplo ilustra la producción de etil 3-(1-oxidopiridin-4-il)-1H-pirazol-5-carboxilato.

[000172] Se cargó un matraz con etil 3-piridin-4-il-1H-pirazol-5-carboxilato (5.04 g, 23.2 mmol) y ácido 3-cloroperoxibenzoico (7.06g, 27.8 mmol) en 70 mL de diclorometano. Después de 2 horas, la reacción se concentró *in vacuo* para retirar la mayor parte del diclorometano. Al residuo se agregó 5% acetato de etilo/hexanos y se filtró la suspensión. El sólido se suspendió en $NaHCO_3$ saturado, se filtró, y se enjuagó con $NaHCO_3$ (saturado). El sólido se suspendió en seguida en NaS_2O_3, se filtró, y luego se enjuagó con agua. El sólido se suspendió en etanol y se concentró para proporcionar un sólido anaranjado-amarillento (4.25 g, 78.0% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.24 (d, 2H), 7.86 (d, 2H), 7.42 (s, 1H), 4.31 (q, 2H), 1.31 (t, 3H); HRMS calculado para (M + H) 234.0873, hallado 234.0877.

EJEMPLO 7

[000173] Este ejemplo ilustra la producción de etil 3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato.

[000174] Una suspensión de etil 3-(1-oxidopiridin-4-il)-1H-pirazol-5-carboxilato (11.16 g, 14.9 mmol) y oxicloruro de fósforo (110 mL, 1.2 mol) se calentó a 106°C durante 48 horas. La mezcla de reacción se concentró, y luego se disolvió en cloroformo (300 mL) y agua helada (300 mL). Se agregó $NaHCO_3$ sólido hasta que ya no se observó espumación, luego se extrajo la solución heterogénea múltiples veces con cloroformo. Las capas orgánicas se secaron sobre $MgSO_4$, se filtraron, y se concentraron. El residuo se trituró con diclorometano. El sólido se filtró y se enjuagó con acetato de etilo, y luego con éter dietílico para proporcionar un sólido amarillo pálido (3.59 g, 29.8% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 14.41 (brs, 1H), 8.44 (d, 1H), 7.98 (s, 1H), 7.88 (d, 1H), 7.61 (s, 1H), 4.33 (q, 2H), 1.32 (t, 3H); HRMS calculado para (M + H) 252.0534, hallado 252.0508.

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EJEMPLO 8

[000175] Este ejemplo ilustra la producción de etil 1-{3-[(terc-butoxicarbonil)-amino]propil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato.

[000176] La síntesis se condujo como en la preparación de etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-piridin-4-il-1H-pirazol-5-carboxilato usando etil 3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (3.36 g, 13.3 mmol), *t*-butóxido de litio (1M en THF, 17.0 mL), *terc*-butil 3-bromopropilcarbamato (3.81 g, 16.0 mmol) y yoduro de sodio (2.39 g, 16.0 mmol). La purificación cromatográfica (25% acetato de etilo/hexano) produjo un sólido blanco (3.29 g, 60.5% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.42 (d, 1H), 7.95 (s, 1H), 7.86 (dd, 1H), 7.67 (s, 1H), 6.85 (dd, 1H), 4.54 (t, 2H), 4.35 (q, 2H), 2.98-2.92 (m, 2H), 1.98-1.88 (m, 2H), 1.36-1.31 (m, 12H); HRMS calculado para (M + H) 409.1637, hallado 409.1634.

EJEMPLO 9

[000177] Este ejemplo ilustra la producción de etil 1-{2-[(terc-butoxicarbonil)-amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato.

[000178] La síntesis se condujo como en la preparación de etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-piridin-4-il-1H-pirazol-5-carboxilato, usando etil 3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (6.00 g, 23.8 mmol), *t*-butóxido de litio (1M en THF, 31.0 mL), *terc*-butil 2-bromoetilcarbamato (6.59 g, 29.4 mmol), y yoduro de sodio (4.41 g, 29.4 mmol). La cromatografía de destello (25% acetato de etilo/hexano) produjo un sólido blanco (6.07 g, 64.6% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.43 (d, 1H), 7.94 (s, 1H), 7.85 (dd, 1H), 7.66 (s, 1H), 6.89 (t, 1H), 4.59 (t, 2H), 4.33 (q, 2H), 3.39-3.32 (m, 2H), 1.36-1.23 (m, 12H); HRMS calculado para (M + H) 395.1481, hallado 395.1512.

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EJEMPLO 10

[000179] Este ejemplo ilustra la producción de 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000180] Se cargó un matraz con etil 1-{3-[(terc-butoxicarbonil)amino] propil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (6.50 g, 15.9 mmol) y 4N HCl/dioxano (45 mL). La mezcla de reacción se agitó durante 1 hora, luego la suspensión se filtró y el sólido se enjuagó con éter dietílico. Este sólido se absorbió en etanol (20 mL) y NH_4OH (40 mL). Después de agitar durante 20 horas, la suspensión se filtró y se enjuagó con etanol y éter dietílico para proporcionar un sólido blanco (3.64 g, 87.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.41 (d, 1H), 8.35 (t, 1H), 7.90 (s, 1H), 7.83 (d, 1H), 7.48 (s, 1H), 4.49 (t, 2H), 3.24-3.18 (m, 2H), 2.20-2.14 (m, 2H), HRMS calculado para (M + H) 263.0694, hallado 263.0689.

EJEMPLO 11

[000181] Este ejemplo ilustra la producción de etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000182] Se cargó un matraz con etil 1-{3-[(terc-butoxicarbonil)amino] propil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.875 g, 2.14 mmol), ácido 3-nitrofenilbórico (0.536 g, 3.21 mmol), 2M Na_2CO_3 (9 mL), tolueno (25 mL), y [1,1' bis(difenilfosfino) ferroceno]dicloropaladio (II), complejo 1:1 con diclorometano [Pd[dppf]Cl_2·CH_2Cl_2 (0.140 g, 0.170 mmol)], luego se purgó con N_2 y se calentó a 90°C durante 20 horas. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua y salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró. La purificación cromatográfica (30% acetato de etilo/hexano) produjo un sólido blanco (0.767 g, 72.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.75 (d, 1H), 8.68 (d, 1H), 8.54 (s, 1H), 8.30 (m, 1H), 7.91 (dd, 1H), 7.84-7.70 (m, 2H), 6.87 (dd, 1H), 4.58 (t, 2H), 4.36 (q, 2H), 3.00-2.95 (m, 2H), 1.98-1.92 (m, 2H), 1.38-1.31 (m, 12H); HRMS calculado para (M + H) 496.2191, hallado 496.2175.

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EJEMPLO 12

[000183] Este ejemplo ilustra la producción de trifluoroacetato de 1-(3-aminopropil)-3-[2-(3 nitrofenil)piridin-4-il]-1H-pirazol-5-carboxamida.

[000184] Se hizo burbujear gas amoníaco en un tubo a presión cargado con etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.084 g, 0.17 mmol) en 10 mL etanol y se enfrió a -78 °C. Luego se selló el tubo y se calentó a 70°C durante 6 días. La mezcla de reacción se concentró *in vacuo*. A este residuo se agregó 4N HCl/ dioxano (6 mL). Después de 1.5 horas, la solución se purificó por Gilson RP HPLC (5-95% acetonitrilo/agua). Las fracciones apropiadas se concentraron en un sólido amarillento claro (0.048 g, 60% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.94 (dd, 1H), 8.81 (d, 1H), 8.60 (d, 1H), 8.43 (s, 1H), 8.36 (dd, 1H), 8.20-8.09 (m, 4H), 7.87-7.74 (m, 3H), 4.66 (t, 2H), 2.86-2.79 (m, 2H), 2.20-2.15 (m, 2H); HRMS calculado para (M + H) 367.1513, hallado 367.1529.

EJEMPLO 13

[000185] Este ejemplo ilustra la producción de diclorhidrato de 1-(3-aminopropil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxamida.

[000186] La síntesis se condujo al igual que para la producción de trifluoroacetato de 1-(3-aminopropil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxamida usando etil 1-{3-[(terc-butoxicarbonil) amino]propil}-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato (0.127 g, 0.254 mmol). El residuo de sal TFA se absorbió en metanol y 4N HCl/dioxano. Después de 20 horas, la suspensión se concentró en un sólido blancuzco (0.069 g, 0.16 mmol): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.90 (d, 1H), 9.78 (s, 1H), 8.87 (d, 1H), 8.69 (s, 1H), 8.46-8.39 (m, 2H), 8.22-8.08 (m, 5H), 7.96-7.89 (m, 2H), 7.82-7.78 (m, 2H), 4.67 (t, 2H), 2.86-2.77 (m, 2H), 2.25-2.16 (m, 2H); HRMS calculado para (M + H) 373.1771, hallado 373.1769.

EJEMPLO 14

[000187] Este ejemplo ilustra la producción de etil 1-{2-[(tertbutoxi-carbonil)amino]etil}-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato.

[000188] La síntesis se condujo como en la preparación de etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.732 g, 1.85 mmol), ácido 3-quinolinilbórico (0.481 g, 2.78 mmol), 2M Na_2CO_3 (7 mL), tolueno (20 mL), y $Pd[dppf]Cl_2$ CH_2Cl_2 (0.121 g, 0.148 mmol). El residuo negro obtenido del desarrollo acuoso se trituró con diclorometano para proporcionar un sólido blancuzco (0.615 g, 68.2% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.72 (s, 1H), 9.14 (s, 1H), 8.78 (d, 1H), 8.62 (s, 1H), 8.15-8.08 (m, 2H), 7.90-7.82 (m, 3H), 7.71-7.66 (m, 1H), 6.94 (t, 1H), 4.64 (t, 2H), 4.37 (q, 2H), 3.39-3.32 (m, 2H), 1.39-1.28 (m, 12H); HRMS calculado para (M + H) 488.2292, hallado 488.2296.

EJEMPLO 15

[000189] Este ejemplo ilustra la producción de trifluoroacetato de 2-{2-[4-(trifluorometoxi)-fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000190] La síntesis se condujo como en la preparación de etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato usando etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.954 g, 2.33 mmol), ácido 3-quinolinilbórico (0.520 g, 3.00 mmol), 2M Na_2CO_3 (10 mL), tolueno (25 mL), y $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.152 g, 0.186 mmol). La cromatografía de destello (25% acetato de etilo/hexano) produjo un sólido color crema (0.593g, 50.7% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.72 (d, 1H), 9.14 (d, 1H), 8.77 (d, 1H), 8.63 (s, 1H), 8.15-8.07 (m, 2H), 7.85-7.82 (m, 3H), 7.69 (dd, 1H), 6.88 (t, 1H), 4.60 (t, 2H), 4.37 (q, 2H), 3.02-2.96 (m, 2H), 2.01-1.93 (m, 2H), 1.39-1.34 (m, 12H); HRMS calculado para (M + H) 502.2449, hallado 502.2419.

EJEMPLO 16

[000191] Este ejemplo ilustra la producción de etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxilato.

[000192] La síntesis se condujo como en la preparación de etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (1.100 g, 2.79 mmol), ácido 4-hidroximetil-fenilbórico (0.550 g, 3.62 mmol), 2M Na_2CO_3 (12 mL), tolueno (32 mL), y $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.182 g, 0.223 mmol). El residuo negro obtenido del desarrollo acuoso se trituró con diclorometano para producir un sólido blancuzco (0.567 g, 43.6% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.67 (d, 1H), 8.32 (s, 1H), 8.15 (d, 2H), 7.78-7.76 (m, 2H), 7.45 (d, 2H), 6.92 (t, 1H), 5.26 (t, 1H), 4.62-4.56 (m, 4H), 4.35 (q, 2H), 3.39-3.35 (m, 2H), 1.36-1.27 (m, 12H); HRMS calculado para (M + H) 467.2289, hallado 467.2259.

EJEMPLO 17

[000193] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(3-aminopropil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000194] La síntesis se condujo como en la preparación de diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato usando etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.763 g, 1.53 mmol) y 4N HCl/dioxano (10 mL). Se obtuvo un sólido amarillo claro (0.685 g, 95.4% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.80 (d, 1H), 8.68 (d, 1H), 8.63 (s, 1H), 8.35 (dd, 1H), 8.13 (brs, 3H), 8.02 (dd, 1H), 7.93 (s, 2H), 7.85 (dd, 1H), 4.68 (t, 2H), 4.37 (q, 2H), 2.87-2.80 (m, 2H), 2.21-2.16 (m, 2H), 1.36 (t, 3H); HRMS calculado para (M + H) 396.1666, hallado 396.1660.

EJEMPLO 18

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[000195] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato.

[000196] La síntesis se condujo como en la preparación de diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato (0.588 g, 1.21 mmol) y 4N HCl/dioxano (12 mL). Se obtuvo un sólido blanco (0.557 g, 100% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.97 (s, 1H), 9.86 (s, 1H), 8.87-8.85 (m, 2H), 8.62 (s, 1H), 8.48-8.41 (m, 5H), 8.15-8.08 (m, 2H), 7.98-7.90 (m, 2H), 4.89 (t, 2H), 4.39 (q, 2H), 3.43-3.36 (m, 2H), 1.37 (t, 3H); HRMS calculado para (M + H), 388.1768, hallado 388.1754.

EJEMPLO 19

[000197] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(3-aminopropil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato.

[000198] La síntesis se condujo al igual que para la preparación de diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato, usando etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato (0.404 g, 0.805 mmol) y 4N HCl/dioxano (10 mL). Se obtuvo un sólido amarillo (0.357g, 93.5% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.92 (d, 1H), 9.72 (d, 1H), 8.84 (d, 1H), 8.79 (s, 1H), 8.40-8.36 (m, 2H), 8.16 (brs, 3H), 8.07-8.00 (m, 2H), 7.93-7.88 (m, 2H), 4.66 (t, 2H), 4.38 (q, 2H), 2.90-2.82 (m, 2H), 2.25-2.16 (m, 2H), 1.37 (t, 3H); HRMS calculado para (M + H) 402.1925, hallado 402.1937.

EJEMPLO 20

[000199] Este ejemplo ilustra la producción de etil 1-(2-aminoetil)-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxilato diclorhidrato.

[000200] La síntesis se condujo al igual que para la preparación de diclorhidrato de etil 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxilato, usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-{2-[4-(hidroximetil)

fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.498 g, 1.07 mmol) y 4N HCl/dioxano (10 mL). Se obtuvo un sólido blanco (0.474g, 100% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.83 (d, 1H), 8.74 (s, 1H), 8.38 (brs, 3H), 8.29-8.20 (m, 3H), 8.08 (s, 1H), 7.57 (d, 2H), 4.90 (t, 2H), 4.62 (m, 2H), 4.39 (q, 2H), 3.40-3.35 (m, 2H), 1.36 (t, 3H); HRMS calculado para (M + H) 367.1765, hallado 367.1751.

EJEMPLO 21

[000201] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitro-fenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000202] Se cargó un matraz con etil 1-{2-[(terc-butoxicarbonil)amino] etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.700 g, 1.78 mmol), ácido 3-nitrofenilbórico (0.446 g, 2.67 mmol), 2M Na_2CO_3 (7 mL), tolueno (20 mL), y [1,1' bis(difenilfosfino)ferroceno]dicloropaladio (II), complejo 1:1 con diclorometano [Pd[dppf]Cl_2·CH_2Cl_2 (0.116 g, 0.142 mmol)], luego se purgó con N_2 y se calentó a 90°C durante 20 horas. La mezcla de reacción se filtró a través de celita y se concentró la capa orgánica. A este residuo se agregó 4N HCl/dioxano (10.0 mL). Después de 2 horas, la mezcla de reacción se purificó por Gilson RP HPLC (5-95% acetonitrilo/agua). Las fracciones apropiadas se concentraron en un residuo pegajoso, el cual se convirtió en la sal HCl usando 4N HCl/dioxano y metanol. Después de agitar 1 hora, la reacción se concentró en un sólido café (0.688 g, 85.1% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.01 (s, 1H), 8.80 (dd, 1H), 8.70-8.64 (m, 2H), 8.35-8.28 (m, 4H), 8.03 (d, 1H), 7.93 (s, 1H), 7.84 (dd, 1H), 4.87 (t, 2H), 4.38 (q, 2H), 3.39-3.33 (m, 2H), 1.36 (t, 3H); HRMS calculado para (M + H) 382.1510, hallado 382.1525.

EJEMPLO 22

[000203] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000204] La síntesis se condujo al igual que para la producción de dicl rhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-

pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.700 g, 1.78 mmol), ácido 4-metoxifenilbórico (0.406 g, 2.67 mmol), 2M Na_2CO_3 (7 mL), tolueno (20 mL), Pd[dppf]Cl_2 CH_2Cl_2 (0.116 g, 0.142 mmol), y 4N HCl/dioxano (10.0 mL). El producto se aisló como un sólido amarillo (0.709 g, 90.7% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.77 (d, 1H), 8.65 (s, 1H), 8.35 (brs, 3H), 8.24 (d, 2H), 8.16 (d, 1H), 8.04 (s, 1H), 7.18 (d, 2H), 4.89 (t, 2H), 4.38 (q, 2H), 3.87 (s, 3H), 3.42-3.38 (m, 2H), 1.36 (t, 3H), HRMS calculado para (M + H) 367.1765, hallado 367.1790.

EJEMPLO 23

[000205] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato.

[000206] La síntesis se condujo al igual que para la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.700 g, 1.78 mmol), ácido 4-trifluorometoxifenilbórico (0.550 g, 2.67 mmol), 2M Na_2CO_3 (7 mL), tolueno (20 mL), Pd[dppf]Cl_2·CH_2Cl_2 (0.116 g, 0.142 mmol), y 4N HCl/dioxano (10.0 mL). El producto se aisló como un sólido amarillento rojizo (0.821 g, 93.5% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.79 (d, 1H), 8.59 (s, 1H), 8.36-8.33 (m, 5H), 8.07 (d, 1H), 7.94 (s, 1H), 7.57 (d, 2H), 4.87 (t, 2H), 4.38 (q, 2H), 3.42-3.38 (m, 2H), 1.36 (t, 3H); HRMS calculado para (M + H) 421.1482, hallado 421.1482.

EJEMPLO 24

[000207] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-{2-[(E)-2-feniletenil]piridin-4-il}-1H-pirazol-5-carboxilato.

[000208] La síntesis se condujo al igual que para la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-

pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil) amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (1.044 g, 2.64 mmol), ácido *trans*-2-fenilvinilbórico (0.587 g, 3.97 mmol), 2M Na_2CO_3 (10 mL), tolueno (30 mL), $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.172 g, 0.211 mmol), y 4N HCl/dioxano (10.0 mL). El producto se aisló como un sólido amarillo (1.213 g, >100% rendimiento, 73.0% pure): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.79-8.72 (m, 2H), 8.36 (brs, 3H), 8.24-8.19 (m, 2H), 7.96 (s, 1H), 7.71 (d, 2H), 7.62-7.45 (m, 5H), 4.89 (t, 2H), 4.39 (q, 2H), 3.41-3.39 (m, 2H), 1.37 (t, 3H); HRMS calculado para (M + H) 363.1816, hallado 363.1807.

EJEMPLO 25

[000209] Este ejemplo ilustra la producción de trifluoroacetato de etil 1-(2-aminoetil)-3-{2-[4-(dimetilamino)fenil]piridin-4-il}-1H-pirazol-5-carboxilato.

[000210] La síntesis se condujo al igual que para la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.758 g, 1.92 mmol), ácido 4-dimetilaminofenilbórico (0.475 g, 2.88 mmol), 2M Na_2CO_3 (8 mL), tolueno (23 mL), $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.126 g, 0.154 mmol), y 4N HCl/dioxano (10.0 mL). La sal TFA se aisló como un sólido amarillo (0.666 g, 70.3% rendimiento): ^1H NMR (DMSO-d_6 /300 MHz) δ 8.64 (d, 1H), 8.46 (s, 1H), 8.07-8.04 (m, 5H), 7.95 (s, 1H), 7.88 (d, 1H), 6.86 (d, 2H), 4.85 (t, 2H), 4.38 (q, 2H), 3.47-3.37 (m, 2H), 3.03 (s, 6H), 1.36 (t, 3H); HRMS calculado para (M + H) 380.2081, hallado 380.2098.

EJEMPLO 26

[000211] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000212] La síntesis se condujo al igual que para la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-

pirazol-5-carboxilato, usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.752g, 1.90 mmol), ácido 3-metoxifenilbórico (0.434 g, 2.86 mmol), 2M Na_2CO_3 (7 mL), tolueno (20 mL), Pd[dppf]Cl_2·CH_2Cl_2 (0.124 g, 0.152 mmol), y 4N HCl/dioxano (10.0 mL). El producto se aisló como un sólido blancuzco (0.500 g, 60.0% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.81 (d, 1H), 8.67 (s, 1H), 8.37 (br s, 3H), 8.22 (d, 1H), 8.04 (s, 1H), 7.82-7.79 (m, 2H), 7.53 (dd, 1H), 7.18 (d, 1H), 4.89 (t, 2H), 4.38 (q, 2H), 3.89 (s, 3H), 3.42-3.36 (m, 2H), 1.36 (t, 3H); HRMS calculado para (M + H) 367.1765, hallado 367.1755.

EJEMPLO 27

[000213] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000214] La síntesis se condujo al igual que para la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato usando etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (0.752g, 1.90 mmol), ácido 3-hidroxifenilbórico (0.629 g, 2.86 mmol), 2M Na_2CO_3 (7 mL), tolueno (20 mL), Pd[dppf]Cl_2·CH_2Cl_2 (0.124 g, 0.152 mmol), y 4N HCl/dioxano (10.0 mL). El producto se aisló como un sólido blancuzco (0.381 g, 46.8% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.80 (d, 1H), 8.62 (s, 1H), 8.37 (brs, 3H), 8.22 (d, 1H), 8.04 (s, 1H), 7.62-7.58 (m, 2H), 7.41 (dd, 1H), 7.05 (dd, 1H), 4.89 (t, 2H), 4.38 (q, 2H), 3.89 (s, 3H), 3.42-3.36 (m, 2H), 1.36 (t, 3H); HRMS calculado para (M + H) 353.1608, hallado 353.1630.

EJEMPLO 28

[000215] Este ejemplo ilustra la producción de 2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000216] Se cargó un matraz con diclorhidrato de etil 1-(2-aminoetil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato (0.303 g, 0.659 mmol), NH_4OH (6 mL) y etanol (3 mL). Después de agitar durante 20 horas, la reacción se filtró, y el sólido se enjuagó con agua, etanol, y éter dietílico

para obtener un sólido blanco (0.178 g, 76.8% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.73 (s, 1H), 9.16 (s, 1H), 8.79 (s, 1H), 8.64 (s, 1H), 8.35 (s, 1H), 8.16-8.08 (m, 2H), 7.90-7.69 (m, 4H), 4.45 (brs, 2H), 3.69 (brs, 2H); HRMS calculado para (M + H) 342.1349, hallado 342.1365.

EJEMPLO 29

[000217] Este ejemplo ilustra la producción de 2-(2-quinolin-3-ilpiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000218] La síntesis se condujo como se hizo para la producción de 2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(3-aminopropil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato (0.144 g, 0.303 mmol), NH_4OH (6mL), y etanol (3 mL). Se obtuvo un sólido blanco (0.046 g, 43% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.72 (d, 1H), 9.16 (d, 1H), 8.77 (d, 1H), 8.61 (s, 1H), 8.35 (br s, 1H), 8.15-8.07 (m, 2H), 7.88-7.79 (m, 2H), 7.71-7.66 (m, 2H), 4.55 (t, 2H), 3.29-3.23 (m, 2H), 2.22-2.18 (m, 2H); HRMS calculado para (M + H) 356.1506, hallado 356.1525.

EJEMPLO 30

[000219] Este ejemplo ilustra la producción de 2-{2-[4-(hidroximetil)fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000220] La síntesis se condujo como se hizo para la producción de 2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(2-aminoetil)-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.202 g, 0.459 mmol), NH_4OH (8 mL), y etanol (4 mL). Se obtuvo un sólido blanco (0.098 g, 66% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.67 (d, 1H), 8.36-8.32 (m, 2H), 8.15 (d, 2H), 7.78 (d, 1H), 7.64 (s, 1H), 7.45 (d, 2H), 5.27 (t, 1H), 4.57 (d, 2H), 4.42 (t, 2H), 3.70-3.66 (m, 2H); HRMS calculado para (M + H) 321.1346, hallado 321.1333.

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EJEMPLO 31

[000221] Este ejemplo ilustra la producción de 2-[2-(3-metoxifenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000222] La síntesis se condujo como se hizo para la producción de 2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.253 g, 0.575 mmol), NH_4OH (8 mL), y etanol (4 mL). Se obtuvo un sólido blancuzco(0.160 g, 86.8% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (s, 1H), 8.37-8.32 (m, 2H), 7.80-7.68 (m, 4H), 7.42 (dd, 1H), 7.03 (d, 1H), 4.42 (t, 2H), 3.86 (s, 3H), 3.69-3.65 (m, 2H); HRMS calculado para (M + H) 321.1346, hallado 321.1344.

EJEMPLO 32

[000223] Este ejemplo ilustra la producción de 2-[2-(3-hidroxifenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000224] La síntesis se condujo como se hizo para la producción de 2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.304 g, 0.715 mmol), NH_4OH (10 mL), y etanol (5 mL). Se obtuvo un sólido blancuzco (0.178 g, 81.1% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.56 (br s, 1H), 8.66 (d, 1H), 8.32-8.28 (m, 2H), 7.79 (s, 1H), 7.63-7.59 (m, 3H), 7.30 (dd, 1H), 6.85 (d, 1H), 4.42 (t, 2H), 3.69-3.64 (m, 2H); HRMS calculado para (M + H) 307.1190, hallado 307.1214.

EJEMPLO 33

[000225] Este ejemplo ilustra la producción de clorhidrato de 2-[2-(3-nitrofenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000226] La síntesis se condujo como se hizo para la producción de trifluoroacetato de 2-piridin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(3-aminopropil)-3-[2-(3-

nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.253 g, 0.540 mmol), NH_4OH (8 mL), y etanol (4 mL). La sal TFA aislada se convirtió en la sal HCl usando metanol y 4N HCl/dioxano. Después de 0.5 hora, la suspensión se concentró y el sólido se enjuagó con éter dietílico para proporcionar un sólido blanco (0.140 g, 65.2% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.78 (d, 1H), 8.65 (d, 1H), 8.60 (s, 1H), 8.39-8.33 (m, 2H), 8.00 (dd, 1H), 7.84 (dd, 1H), 7.74 (s, 1H), 4.54 (t, 2H), 3.27-3.21 (m, 2H), 2.20-2.15 (m, 2H); HRMS calculado para (M + H) 342.1349, hallado 342.1365.

EJEMPLO 34

[000227] Este ejemplo ilustra la producción de trifluoroacetato de 2-{2-[4-(trifluorometoxi)-fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000228] La síntesis se condujo como se hizo para la producción de trifluoroacetato de 2-piridin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(2-aminoetil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.439 g, 0.889 mmol), NH_4OH (8 mL), y etanol (4 mL). Se obtuvo un sólido blancuzco (0.181 g, 43.0% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.72 (d, 1H), 8.45 (s, 1H), 8.33-8.30 (m, 3H), 7.88 (d, 1H), 7.69 (s, 1H), 7.51 (d, 2H), 4.43 (q, 2H), 3.70-3.64 (m, 2H); HRMS calculado para (M + H) 375.1063, hallado 375.1068.

EJEMPLO 35

[000229] Este ejemplo ilustra la producción de trifluoroacetato de 2-{2-[(E)-2-fenilvinil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000230] La síntesis se condujo como se hizo para la producción de trifluoroacetato de 2-piridin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(2-aminoetil)-3-{2-[(E)-2-fenilvinil]piridin-4-il}-1H-pirazol-5-carboxilato (0.610 g, 1.40 mmol), NH_4OH (10 mL), y etanol (5 mL). Se obtuvo un sólido amarillo (0.352 g,

58.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (d, 1H), 8.40 (br s, 2H), 7.97-7.92 (m, 2H), 7.71-7.68 (m, 3H), 7.49-7.37 (m, 4H), 4.45 (t, 2H), 3.70-3.66 (m, 2H); HRMS calculado para (M + H) 317.1397, hallado 317.1405.

EJEMPLO 36

[000231] Este ejemplo ilustra la producción de trifluoroacetato de 2-{2-[4-(dimetilamino)fenil]-piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000232] La síntesis se condujo como se hizo para la producción de trifluoroacetato de 2-piridin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando trifluoroacetato de etil 1-(2-aminoetil)-3-{2-[4-(dimetilamino)fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.350 g, 708 mmol), NH_4OH (8 mL), y etanol (4 mL). Se obtuvo un sólido amarillo (0.204 g, 64.5% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.61 (d, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 8.03 (d, 2H), 7.96 (d, 1H), 7.86 (s, 1H), 6.88 (d, 2H), 4.46 (t, 2H), 3.71-3.66 (m, 2H), 3.05 (s, 6H); HRMS calculado para (M + H) 334.1662, hallado 334.1673.

EJEMPLO 37

[000233] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(4-metoxifenil)-piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000234] La síntesis se condujo como se hizo para la producción de trifluoroacetato de 2-piridin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(2-aminoetil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.368 g, 0.838 mmol), NH_4OH (8 mL), y etanol (4 mL). Se obtuvo un sólido blanco (0.225 g, 61.8% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (d, 1H), 8.45 (s, 1H), 8.36 (s, 1H), 8.13 (d, 2H), 7.93 (d, 1H), 7.76 (s, 1H), 7.12 (d, 2H), 4.44 (t, 2H), 3.85 (s, 3H), 3.71-3.66 (m, 2H); HRMS calculado para (M + H) 321.1346, hallado 321.1359.

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EJEMPLO 38

[000235] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(3-nitrofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000236] La síntesis se condujo como se hizo para la producción de trifluoroacetato de 2-piridin-4-il-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona usando diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.350 g, 0.771 mmol), NH_4OH (8 mL), y etanol (4 mL). Se obtuvo un sólido color crema (0.152 g, 43.8% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (s, 1H), 8.75 (d, 1H), 8.66 (d, 1H), 8.32-8.28 (m, 2H), 7.89 (d, 1H), 7.81 (dd, 1H), 7.73 (s, 1H), 4.43 (t, 2H), 3.70-3.65 (m, 2H); HRMS calculado para (M + H) 336.1091, hallado 336.1068.

EJEMPLO 39

[000237] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(3,4-difluorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000238] La síntesis se condujo al igual que para la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato usando 2-(2-cloropiridin-4-il)-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona (0.175 g, 0.702 mmol), ácido 3,4-difluorofenilbórico (0.167 g, 1.05 mmol), 2M Na_2CO_3 (2 mL), tolueno (7 mL), y Pd[dppf]Cl_2·CH_2Cl_2 (0.046 g, 0.057 mmol). La sal TFA se aisló como un sólido blanco (0.076 g, 25% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.68 (d, 1H), 8.42 (s, 1H), 8.32-8.23 (m, 2H), 8.09 (d, 1H), 7.82 (s, 1H), 7.69 (s, 1H), 7.55 (dd, 1H), 4.41 (t, 2H), 3.69-3.64 (m, 2H); HRMS calculado para (M + H) 327.1052, hallado 327.1078.

EJEMPLO 40

[000239] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(3,4-diclorofenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000240] La síntesis se condujo al igual que para la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-

pirazol-5-carboxilato usando 2-(2-cloropiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona (0.175 g, 0.702 mmol), ácido 3,4-diclorofenilbórico (0.200 g, 1.05 mmol), 2M Na_2CO_3 (2 mL), tolueno (7 mL), y $Pd[dppf]Cl_2 \cdot CH_2Cl_2$ (0.046 g, 0.057 mmol). La sal TFA se obtuvo como un sólido gris (0.016 g, 4.9% rendimiento): ^1H NMR (DMSO-d_6, TFA / 300 MHz) δ 8.81 (d, 1H), 8.66 (s, 1H), 8.42-8.34 (m, 2H), 8.28-8.18 (m, 2H), 7.87-7.85 (m, 2H), 4.45 (t, 2H), 3.71-3.64 (m, 2H), HRMS calculado para (M + H) 359.0461, hallado 359.0476.

EJEMPLO 41

[000241] Este ejemplo ilustra la producción de diclorhidrato de ácido 1-(3-aminopropil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxílico.

[000242] La síntesis se condujo al igual que para la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.253 g, 0.539 mmol) y $LiOH \cdot H_2O$ (0.0679 g, 1.62 mmol. La sal TFA aislada era un sólido pegajoso, y por lo tanto se convirtió en la sal HCl usando metanol y 4N HCl/dioxano. Después de 0.5 hora, la suspensión se concentró y el sólido se enjuagó con éter dietílico para proporcionar un sólido blanco (0.223 g, 94.6% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.00 (dd, 1H), 8.79 (d, 1H), 8.68 (d, 1H), 8.60 (s, 1H), 8.34 (dd, 1H), 8.11 (brs, 3H), 7.99 (dd, 1H), 7.88-7.81 (m, 2H), 4.68 (t, 2H), 2.86-2.79 (m, 2H), 2.20-2.15 (m, 2H); HRMS calculado para (M + H) 368.1353, hallado 368.1336.

EJEMPLO 42

[000243] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(2-aminoetil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxílico.

[000244] La síntesis se condujo al igual que para la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando diclorhidrato de etil 1-(2-aminoetil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato (0.211 g, 0.457 mmol) y $LiOH \cdot H_2O$

(0.077 g, 1.8 mmol). Se obtuvo un sólido rosado (0.150 g, 69.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.75 (s, 1H), 9.23 (d, 1H), 8.82 (d, 1H), 8.69 (s, 1H), 8.17-8.10 (m, 2H), 8.01-7.94 (m, 3H), 7.89-7.83 (m, 2H), 7.72 (dd, 1H), 4.86 (t, 2H), 3.44-3.38 (m, 2H); HRMS calculado para (M + H) 360.1455, hallado 360.1466.

EJEMPLO 43

[000245] Este ejemplo ilustra la producción de diclorhidrato de ácido 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxílico.

[000246] La síntesis se condujo al igual que para la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.262 g, 0.516 mmol) y LiOH•H_2O (0.097 g, 2.3 mmol). La sal TFA aislada se convirtió en la sal HCl usando metanol y 4N HCl/dioxano. Después de 0.5 hora, la suspensión se concentró y el sólido se enjuagó con éter dietílico para proporcionar a sólido amarillo (0.102 g, 46.5% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) 89.01 (s, 1H), 8.80 (d, 1H), 8.70-8.64 (m, 2H), 8.35-8.28 (m, 4H), 8.02 (d, 1H), 7.89-7.82 (m, 2H), 3.39-3.33 (m, 2H); HRMS calculado para (M + H) 354.1197, hallado 354.1176.

EJEMPLO 44

[000247] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(2-aminoetil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico.

[000248] La síntesis se condujo al igual que para la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando diclorhidrato de etil 1-(2-aminoetil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.260 g, 0.591 mmol) y LiOH•H_2O (0.099 g, 2.4 mmol). Se obtuvo un sólido amarillo pálido (0.212 g, 79.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.69 (d, 1H), 8.42 (s, 2H), 8.15 (d, 1H), 8.00 (br s, 3H), 7.88-7.84 (m, 2H), 7.09 (d, 2H), 4.84 (t, 2H), 3.84 (s, 3H), 3.38-3.42 (m, 2H); HRMS calculado para

(M + H) 339.1452, hallado 339.1472.

EJEMPLO 45

[000249] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(2-aminoetil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000250] La síntesis se condujo al igual que para la preparación trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando diclorhidrato de etil 1-(2-aminoetil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.257 g, 0.521 mmol) y LiOH•$H_2$0 (0.097 g, 2.3 mmol). Se obtuvo un sólido color crema (0.088 g, 34% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.73 (d, 1H), 8.50 (s, 1H), 8.32 (d, 2H), 8.01 (brs, 3H), 7.88 (d, 1H), 7.81 (s, 1H), 7.51 (d, 2H), 4.84 (t, 2H), 3.42-3.38 (m, 2H); HRMS calculado para (M + H) 393.1169, hallado 393.1189.

EJEMPLO 46

[000251] Este ejemplo ilustra la producción trifluoroacetato de ácido 1-(2-aminoetil)-3-{2-[4-(dimetilamino)fenil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000252] La síntesis se condujo al igual que para la preparación trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico usando trifluoroacetato de etil 1-(2-aminoetil)-3-{2-[4-(dimetilamino) fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.238 g, 0.482 mmol) y LiOH•H_2O (0.088 g, 2.1 mmol). Se obtuvo un sólido anaranjado brillante (0.150 g, 67.0% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.64 (d, 1H), 8.46 (s, 1H), 8.07-8.04 (m, 5H), 7.91-7.88 (m, 2H), 6.86 (d, 2H), 4.86 (t, 2H), 3.43-3.37 (m, 2H), 3.03 (s, 6H); HRMS calculado para (M + H) 352.1768, hallado 352.1770.

EJEMPLO 47

[000253] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-

(2-aminoetil)-3-{2-[(E)-2-feniletenil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000254] La síntesis se condujo como en la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando diclorhidrato de etil 1-(2-aminoetil)-3-{2-[(E)-2-fenilvinil]piridin-4-il}-1H-pirazol-5-carboxilato (0.311 g, 0.714 mmol) y $LiOH \cdot H_2O$ (0.120 g, 2.86 mmol). La sal TFA se aisló como un sólido amarillo claro (0.220 g, 68.7% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.68 (d, 1H), 8.26 (s, 1H), 8.03 (br s, 3H), 7.89-7.84 (m, 2H), 7.73-7.68 (m, 3H), 7.45-7.36 (m, 4H), 4.89 (t, 2H), 3.41-3.39 (m, 2H); HRMS calculado para (M + H) 335.1503, hallado 335.1496.

EJEMPLO 48

[000255] Este ejemplo ilustra la producción de diclorhidrato de ácido 1-(3-aminopropil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxílico.

[000256] La síntesis se condujo al igual que para la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando diclorhidrato de etil 1-(3-aminopropil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxilato (0.134 g, 0.282 mmol) y $LiOH \cdot H_2O$ (0.047 g, 1.1 mmol). La sal TFA se convirtió en la sal HCl usando metanol y 4N HCl/dioxano. Después de 0.5 hora, la suspensión se concentró y el sólido se enjuagó con éter dietílico para proporcionar un sólido amarillo (0.086 g, 68% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.92 (d, 1H), 9.95 (s, 1H), 9.83 (s, 1H), 8.44-8.41 (m, 2H), 8.17-8.09 (m, 4H), 8.03 (d, 1H), 7.94 (dd, 1H), 7.86 (s, 1H), δ 4.69 (t, 2H), 2.90-2.82 (m, 2H), 2.25-2.16 (m, 2H); HRMS calculado para (M + H) 374.1612, hallado 374.1622.

EJEMPLO 49

[000257] Este ejemplo ilustra la producción de diclorhidrato de ácido 1-(2-aminoetil)-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000258] La síntesis se condujo al igual que para la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-

carboxílico, usando diclorhidrato de etil 1-(2-aminoetil)-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.167 g, 0.379 mmol) y LiOH•H_2O (0.064 g, 1.5 mmol). La sal TFA se convirtió en la sal HCl usando metanol y 4N HCl/dioxano. Después de 0.5 hora, la suspensión se concentró y el sólido se enjuagó con éter dietílico para proporcionar un sólido rosado pálido (0.069 g, 70% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.80 (d, 1H), 8.67 (s, 1H), 8.33 (brs, 3H), 8.22-8.19 (m, 3H), 8.00 (s, 1H), 7.55 (d, 2H), 4.89 (t, 2H), 4.62 (m, 2H), 3.40-3.35 (m, 2H); HRMS calculado para (M + H) 339.1452, hallado 339.1435.

EJEMPLO 50

[000259] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(2-aminoetil)-3-[2-(3-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico.

[000260] La síntesis se condujo al igual que para la preparación de trifluoroacetato de ácido 1-(2-aminoetil)-3-piridin-4-il-1H-pirazol-5-carboxílico, usando diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato (0.179 g, 0.407 mmol) y LiOH•H_2O (0.105 g, 2.50 mmol). Se obtuvo un sólido blancuzco (0.168 g, 91.2% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.72 (d, 1H), 8.43 (s, 1H),
8.00 (br s, 3H), 7.88 (d, 1H), 7.83 (s, 1H), 7.78-7.74 (m, 2H), 7.44 (dd, 1H), 7.06 (dd, 1H), 4.84 (t, 2H), 3.85 (s, 3H), 3.44-3.38 (m, 2H); HRMS calculado para (M + H) 339.1452, hallado 339.1469.

EJEMPLO 51

[000261] Este ejemplo ilustra la producción de trifluoroacetato de 1-(2-aminoetil)-N-hidroxi-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxamida.

[000262] Metóxido de sodio recién preparado (3.48 M, 0.27 mL) se agregó gota a gota a una solución en agitación de clorhidrato de hidroxilamina (0.039 mL, 0.94 mmol) en metanol (1 mL) mantenida a 40°C. La suspensión blanca se enfrió a la temperatura de la sala, y en seguida se

agregó una solución de etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxilato (0.400 g, 0.857 mmol) en metanol (5 mL). Después de agitar durante 48 horas, se agregaron 7 mL de 4N HCl (acuoso) y la reacción se agitó durante 20 horas. La purificación por Gilson RP HPLC (5-95% acetonitrilo/agua) produjo un sólido rosado (0.129 g, 32.1% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 11.53 (brs, 1H), 8.73 (d, 1H), 8.31 (s, 1H), 8.11- 8.01 m, 5H), 7.75 (d, 1H), 7.52-7.46 (m, 3H), 4.77 (t, 2H), 4.58 (s, 2H), 3.42-3.35 (m, 2H); HRMS calculado para (M + H) 354.1561, hallado 354.1538.

EJEMPLO 52

[000263] Este ejemplo ilustra la producción de clorhidrato de 2-[2-(1 H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000264] Se cargó un matraz con 1.2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol), pirazol (0.325 g, 4.78 mmol), e hidruro de sodio (0.229 g, 5.73 mmol) en 6 mL de DMF anhidro y se agitó bajo N_2 durante 60 horas a 138°C. Entonces se atemperó la reacción con 1N HCl acuoso y se purificó por Gilson RP HPLC (5-95% acetonitrilo/agua). Las fracciones apropiadas se concentraron y se convirtieron en la sal HCl usando metanol y 4N HCl/dioxano. La mezcla se concentró en un sólido amarillo claro (0.028 g, 8.2% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.64 (d, 1H), 8.48 (d, 1H), 8.35 (brs, 2H), 7.85 (s, 1H), 7.77 (d, 1H), 7.45 (s, 1H), 6.59 (s, 1H), 4.53 (t, 2H), 3.26-3.20 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculado para (M + H) 295.1302, hallado 295.1285.

EJEMPLO 53

[000265] Este ejemplo ilustra la producción de clorhidrato de 2-[2-(1H-imidazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000266] La síntesis se condujo al igual que para la producción de

clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona usando 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol) e imidazol, derivado de sodio (0.431 g, 4.78 mmol). Se obtuvo un sólido blanco (0.074 g, 23% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 10.0 (s, 1H), 8.62 (d, 1H), 8.55 (s, 1H), 8.48 (s, 1H), 8.41 (brs, 1H), 7.99 (d, 1H), 7.90 (s, 1H), 7.65 (s, 1H), 4.53 (t, 2H), 3.28-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculado para (M + H) 295.1302, hallado 295.1290.

EJEMPLO 54

[000267] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(1H-pirrol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000268] La síntesis se condujo al igual que para la producción de clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ons, usando 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol), pirrol (0.334 mL, 4.78 mmol), e hidruro de sodio (0.229 g, 5.73 mmol). La sal TFA se aisló como un sólido negro (0.128 g, 32.7% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.42 (d, 1H), 8.34 (br s, 1H), 8.05 (s, 1H), 7.79 (br s, 2H), 7.67-7.64 (m, 2H), 6.30 (br s, 2H), 4.52 (t, 2H), 3.28-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculado para (M+H) 294.1349, hallado 294.1348.

EJEMPLO 55

[000269] Este ejemplo ilustra la producción de 2-[2-(4-metil-1H-imidazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-one clorhidrato.

[000270] La síntesis se condujo al igual que para la producción de clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona, usando 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol), 4-

metilimidazol (0.393 g, 4.78 mmol), e hidruro de sodio (0.229 g, 5.73 mmol). Se obtuvo un sólido café (0.053 g, 16% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.88 (s, 1H), 8.60 (d, 1H), 8.40 (br s, 2H), 8.28 (s, 1H), 7.97 (d, 1H), 7.63 (s, 1H), 4.53 (t, 2H), 3.29-3.22 (m, 2H), 2.36 (s, 3H), 2.22-2.16 (m, 2H); HRMS calculado para (M + H) 309.1458, hallado 309.1462.

EJEMPLO 56

[000271] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(4-fenil-1H-imidazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona.

[000272] La síntesis se condujo al igual que para la producción de clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,67,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona, usando 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol), 4-fenilimidazol (0.690 g, 4.78 mmol), e hidruro de sodio (0.229 g, 5.73 mmol). La sal TFA se aisló as un sólido blanco (0.060 g, 13% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) 89.17 (s, 1H), 8.76 (s, 1H), 8.57 (d, 1H), 8.37-8.32 (m, 2H), 7.93-7.88 (m, 3H), 7.65 (s, 1H), 7.47 (dd, 2H), 7.36-7.34 (m, 1H), 4.54 (t, 2H), 3.29-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculado para (M + H) 371.1615, hallado 371.1626.

EJEMPLO 57

[000273] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(4-metil-1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona.

[000274] La síntesis se condujo como se hizo para la producción de clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona, usando 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol), 4-metilpirazol (0.40 mL, 4.8 mmol), e hidruro de sodio (0.229 g, 5.73 mmol). La sal TFA se aisló como un sólido blanco (0.068 g, 16% rendimiento): ^{1}H

NMR (DMSO-d_6 / 300 MHz) δ 8.45-8.29 (m, 4H), 7.72 (m, 1H), 7.66 (s, 1H), 7.42 (s, 1H), 4.54 (t, 2H), 3.25-3.20 (m, 2H), 2.20-2.11 (m, 5H); HRMS calculado para (M + H) 309.1458, hallado 309.1448.

EJEMPLO 58

[000275] Este ejemplo ilustra la producción de clorhidrato de 2-[2-(1H-1,2,4-triazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000276] La síntesis se condujo como se hizo para la producción de clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona, usando 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol) y 1,2,4-triazol, derivado de sodio (0.435 g, 4.78 mmol). Se obtuvo un sólido blanco (0.157 g, 48.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.40 (s, 1H), 8.55 (d, 1H), 8.37-8.33 (m, 2H), 8.27 (s, 1H), 7.90 (dd, 1H), 7.50 (s, 1H), 4.53 (t, 2H), 3.25-3.20 (m, 2H), 2.22-2.14 (m, 2H); HRMS calculado para (M + H) 296.1254, hallado 296.1244.

EJEMPLO 59

[000277] Este ejemplo ilustra la producción de clorhidrato de 2-[2-(1H-1,2,3-triazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000278] La síntesis se condujo como se hizo para la producción de clorhidrato de 2-[2-(1H-pirazol-1-il)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona, usando 2-(2-cloropiridin-4-il)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.251 g, 0.960 mmol), 1,2,3-triazole (0.28 mL, 4.8 mmol), e hidruro de sodio (0.229 g, 5.73 mmol). Se obtuvo un sólido blanco (0.118 g, 36.0% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.89 (s, 1H), 8.61 (d, 1H), 8.52 (s, 1H), 8.37 (br s, 1H), 8.01-7.96 (m, 2H), 7.55 (s, 1H), 4.54 (t, 2H), 3.29-3.22 (m, 2H), 2.22-2.16 (m, 2H); HRMS calculado para (M + H) 296.1254, hallado 296.1243.

EJEMPLO 60

[000279] Este ejemplo ilustra la producción de etil 1-{3-[(terc-butoxicarbonil)-amino]propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxilato.

[000280] A una solución enfriada (0°C) de etil 3-(4-metoxifenil)-1H-pirazol-5-carboxilato en DMF anhidro (35 mL) se agregó t-butóxido de litio (1M in THF, 6.6 mL) gota a gota. La reacción se agitó durante 30 min, y luego se agregó gota a gota una solución de *terc*-butil 3-bromopropilcarbamato (1.57 g, 6.60 mmol) y yoduro de sodio (0.989 g, 6.60 mmol) en DMF anhidro (10 mL). La reacción se dejó agita y calentar a la temperatura de la sala durante 4 horas. La reacción se vertió entonces en agua y salmuera y se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron, y se concentraron. La purificación cromatográfica (15% acetato de etilo/hexano) produjo un aceite amarillo (1.13 g, 63.7% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 7.81 (d, 2H), 7.27 (s, 1H), 6.87 (t, 1H), 6.79 (d, 2H), 4.52 (t, 2H), 4.37 (q, 2H), 3.80 (s, 3H), 3.30-2.94 (m, 2H), 1.96-1.91 (m, 2H), 1.39-1.33 (m, 12H); HRMS calculado para (M + H) 404.2180, hallado 404.2190.

EJEMPLO 61

[000281] Este ejemplo ilustra la producción de ácido 1-{3-[(terc-butoxicarbonil)-amino]propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxílico.

[000282] Una solución de etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxilato (0.467 g, 1.16 mmol) y $LiOH•H_2O$ (0.097 g, 2.32 mmol) en 12 mL de THF/H_2O (1:1) se agitó a la temperatura de la sala durante 3 horas. La mezcla de reacción se concentró en la fase acuosa, luego se diluyó con 0.1 N HCl y se extrajo tres veces con acetato de etilo. Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron, y se concentraron en un sólido amarillo pálido (0.359 g, 82.3% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 7.71 (d, 2H),

7.01 -6.94 (m, 3H), 6.88 (s, 1H), 4.62 (t, 2H), 3.80 (s, 3H), 2.94-2.90 (m, 2H), 1.91-1.84 (m, 2H), 1.39 (s, 9H); HRMS calculado para (M + H) 376.1867, hallado 376.1906.

EJEMPLO 61

[000283] Este ejemplo ilustra la producción de diclorhidrato de ácido 1-(3-aminopropil)-3-(4-hidroxifenil)-1H-pirazol-5-carboxílico.

[000284] A una solución enfriada (-78 °C) de ácido 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxílico (0.262 g, 0.70 mmol) en diclorometano anhidro (7 mL) se agregó tribromuro de boro (1,0M in CH_2Cl_2, 7.0 mL) gota a gota. Después de 1 hora, la reacción se atemperó cuidadosamente con agua, luego se concentró en una capa acuosa y se purificó por Gilson RP HPLC (5-95% acetonitrilo/agua). Las fracciones apropiadas se concentraron. El residuo se convirtió en la sal HCl usando 4N HCl/dioxano y metanol. Después de agitar 1 hora, la mezcla se concentró en un sólido blanco (0.238 g, 100% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.07 (br s, 3H), 7.67 (d, 2H), 7.18 (s, 1H), 6.83 (d, 2H), 4.59 (t, 2H), 2.84-2.78 (m, 2H), 2.18-2.08 (m, 2H); HRMS calculado para (M + H) 262.1186, hallado 262.1195.

EJEMPLO 62

[000285] Este ejemplo ilustra la producción de clorhidrato de etil 1-(3-aminopropil)-3-(4-metoxifenil)-1H-pirazol-5-carboxilato.

[000286] A un matraz cargado con etil 1-{3-[(terc-butoxicarbonil) amino]propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxilato (0.588 g, 1.46 mmol) se agregó 4N HCl/dioxano (5 mL). Después de 1 hora, la mezcla de reacción se filtró y se enjuagó con éter dietílico para producir un sólido blanco (0.443 g, 89.4% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.06 (br s, 3H), 7.81 (d, 2H), 7.32 (s, 1H), 7.00 (d, 2H), 4.61 (t, 2H), 4.37 (q, 2H), 3.80 (s, 3H), 2.87-2.80 (m, 2H), 2.20-2.11 (m, 2H), 1.36 (t, 3H), HRMS calculado para (M + H) 304.1656, hallado 304.1665.

EJEMPLO 63

[000287] Este ejemplo ilustra la producción de 2-(4-metoxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000288] A un matraz cargado con clorhidrato de etil 1-(3-aminopropil)-3-(4-metoxifenil)-1H-pirazol-5-carboxilato (0.418 g, 1.23 mmol) se agregaron NH_4OH (20 mL) y etanol (10 mL). Después de agitar durante 18 horas, la reacción se filtró, y el sólido blanco se enjuagó con éter dietílico para proporcionar un sólido blanco (0.243 g, 76.8% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.28 (br s, 1H), 7.77 (d, 2H), 7.10 (s, 1H), 6.98 (d, 2H), 4.45 (t, 2H), 3.80 (s, 3H), 3.26-3.21 (m, 2H), 2.20-2.13 (m, 2H); HRMS calculado para (M + H) 258.1242, hallado 258.1237.

EJEMPLO 64

[000289] Este ejemplo ilustra la producción de 2-(4-hidroxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000290] La síntesis se condujo como se hizo para la preparación de diclorhidrato de ácido 1-(3-amino-propil)-3-(4-hidroxifenil)-1H-pirazol-5-carboxílico usando clorhidrato de etil 1-(3-aminopropil)-3-(4-metoxifenil)-1H-pirazol-5-carboxilato (0.182 g, 0.70 mmol) y tribromuro de boro (7.0 mL). La purificación por Gilson RP HPLC (5-95% acetonitrilo / agua) produjo un sólido blanco (0.078 g, 46% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 9.55 (brs, 1H), 8.25 (brs, 1H), 7.65 (d, 2H), 7.03 (s, 1H), 6.80 (d, 2H), 4.44 (t, 2H), 3.26-3.21 (m, 2H), 2.18-2.13 (m, 2H); HRMS calculado para (M + H) 244.1081, hallado 244.1049.

EJEMPLO 65

[000291] Este ejemplo ilustra la producción de etil 1-{3-[(terc-butoxi-carbonil)amino]propil}-3-(3-metoxifenil)-1H-pirazol-5-carboxilato.

[000292] La síntesis se condujo como se hizo para la preparación de etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxilato, usando etil 3-(3-metoxifenil)-1H-pirazol-5-carboxilato (2.01 g, 8.17 mmol), *t*-butóxido de litio (12.3 mL), *terc*-butil 3-

bromopropilcarbamato (2.92 g, 12.3 mmol) y yoduro de sodio (1.84 g, 12.3 mmol). La cromatografía de destello (12% acetato de etilo/hexano) produjo un aceite amarillo, el cual se trituró con éter dietílico para producir un sólido amarillo pálido (1.47 g, 45.0% rendimiento): HRMS calculado para (M + H) 404.2180, hallado 404.2206.

EJEMPLO 66

[000293] Este ejemplo ilustra la producción de ácido 1-{3-[(terc-butoxicarbonil)-amino]propil}-3-(3-metoxifenil)-1H-pirazol-5-carboxílico.

[000294] La síntesis se condujo como se hizo para la preparación de ácido 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(4-metoxifenil)-1H-pirazol-5-carboxílico usando etil 1-{3-[(terc-butoxicarbonil) amino]propil}-3-(3-metoxifenil)-1H-pirazol-5-carboxilato (0.610 g, 1.51 mmol) y $LiOH \cdot H_2O$ (0.127 g, 3.02 mmol). Se obtuvo un sólido blancuzco (0.565g, 100% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 13.47 (br s, 1H), 7.46-7.32 (m, 4H), 6.93-6.86 (m, 2H), 4.56 (t, 2H), 3.83 (s, 3H), 3.01-2.95 (m, 2H), 1.96-1.90 (m, 2H), 1.39 (s, 9H); HRMS calculado para (M + H) 376.1873, hallado 376.1896.

EJEMPLO 67

[000295] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(3-aminopropil)-3-(3-hidroxifenil)-1H-pirazol-5-carboxílico.

[000296] La síntesis se condujo como se hizo para la preparación de diclorhidrato de ácido 1-(3-amino-propil)-3-(4-hidroxifenil)-1H-pirazol-5-carboxílico, usando ácido 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(3-metoxifenil)-1H-pirazol-5-carboxílico (0.496 g, 1.32 mmol) y tribromuro de boro (1.0M en CH_2Cl_2, 13.0 mL). La sal TFA se aisló como un sólido blancuzco (0.353 g, 71.3% rendimiento): ^1H NMR (DMSO-d_6 / 300 MHz) δ 13.62 (brs, 1H), 9.56 (brs, 1H), 7.80 (brs, 3H), 7.27-7.23 (m, 4H), 6.77 (d, 1H), 4.63 (t, 2H), 2.89-2.81 (m, 2H), 2.17-2.07 (m, 2H); HRMS calculado para (M + H) 262.1192, hallado 262.1223.

EJEMPLO 68

[000297] Este ejemplo ilustra la producción de 2-(3-metoxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000298] La síntesis se condujo como se hizo para la preparación de clorhidrato de etil 1-(3-aminopropil)-3-(4-metoxifenil)-1H-pirazol-5-carboxilato, usando etil 1-{3-[(terc-butoxicarbonil)amino]propil}-3-(3-metoxifenil)-1H-pirazol-5-carboxilato (0.737 g, 1.83 mmol) y 4N HCl/dioxano (10 mL). El aceite incoloro resultante se sometió a las condiciones descritas para la producción de 2-(4-metoxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona, usando NH_4OH (12 mL) y etanol (6 mL). Se obtuvo un sólido blancuzco: ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 8.29 (br s, 1H), 7.34-7.45 (m, 3H), 7.23 (s, 1H), 6.90 (dd, 1H), 4.48 (t, 2H), 3.83 (s, 3H), 3.26-3.21 (m, 2H), 2.22-2.14 (m, 2H); HRMS calculado para (M + H) 258.1242, hallado 258.1232.

EJEMPLO 69

[000299] Este ejemplo ilustra la producción de 2-(3-hidroxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000300] La síntesis se condujo como se hizo para la preparación de diclorhidrato de ácido 1-(3-amino-propil)-3-(4-hidroxifenil)-1H-pirazol-5-carboxílico, usando 2-(3-metoxifenil)-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona (0.325 g 1.26 mmol) y tribromuro de boro (13.0 mL). La purificación por Gilson RP HPLC (5-95% acetonitrilo / agua) produjo un sólido blanco (0.194 g, 63.3% rendimiento): ^{1}H NMR (DMSO-d_6 / 300 MHz) δ 9.45 (br s, 1H), 8.28 (brs, 1H), 7.28-7.19 (m, 3H), 7.08 (s, 1H), 6.75-6.72 (m, 1H), 4.47 (t, 2H), 3.26-3.21 (m, 2H), 2.20-2.16 (m, 2H); HRMS calculado para (M + H) 244.1086, hallado 244.1115.

EJEMPLO 70

[000301] Este ejemplo ilustra la producción de clorhidrato de ácido 1-(3-{[2-(4-bromofenil)etil]-amino}propil)-3-piridin-4-il-1H-pirazol-5-

carboxílico.

[000302] Un matraz de fondo redondo con un solo cuello se cargó con etil 3-piridin-4-il-1H-pirazol-5-carboxilato (1.0 g, 4.6 mmol) y 30 mL DMF. La solución se enfrió a -40°C en un baño de hielo seco / CH_3CN. Se agregó gota a gota una solución 1M de *t*-butóxido de litio en THF (6.9 mL, 6.9 mmol) durante 5 minutos. Después de agitar a -40°C durante 30 minutos, se agregó gota a gota durante 5 minutos una solución de 3-[[2-(4-bromofenil)etil](terc-butoxicarbonil)amino]propilmetanosulfonato (3.0 g, 6.9 mmol) en 10 mL DMF. Después de 1 hora, la reacción se dejó calentare a temperatura ambiente y se agitó durante 18 horas. La mezcla de reacción se concentró *in vacuo*, y el residuo se absorbió en acetato de etilo. Esto se lavó 3 veces con salmuera, se secó sobre sulfato de magnesio, y se concentró en un aceite café. El aceite se trató con 20 mL de una solución 4 N de HCl en dioxano, y se agitó durante 30 minutos para retirar el grupo protector. Después de concentrar *in vacuo* la mezcla cruda se trató con 20 mL de una solución 2.5 N de hidróxido de sodio. La mezcla se calentó a 100 °C durante 1 hora para hidrolizar el éster. La mezcla de producto resultante se concentró *in vacuo* en la mitad del volumen, y luego se cromatografió en una HPLC de fase reversa Gilson eluyendo con una gradiente de acetonitrilo/agua (5-70% CH_3CN durante 15 minutos) para proporcionar el producto deseado como una sal TFA. La sal se absorbió en metanol, y se trató con 10 mL de una solución 4 N de HCl en dioxano para convertirla en la sal HCl. La cristalización de éter dietílico produjo 1.30g (56%) del compuesto del título como un sólido amarillento. LCMS mostró un pico único con m/z 429 (M+H). ^{1}H nmr (DMSO-d_6 / 300 MHz) δ 9.48 (broad s, 2H), 8.94 (d, 2H), 8.46 (d, 2H), 7.90 (s, 1H), 7.50 (d, 2H), 7.22 (d, 2H), 4.71 (t, 2H), 3.20-2.88 (m, 6H), 2.30 (m, 2H), ES^+ HRMS calculado para M+H 429.0921, observado 429.0934.

EJEMPLO 71

[000303] Este ejemplo ilustra la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico.

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[000304] Paso 1. Preparación de clorhidrato de etil 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000305] Este compuesto se preparó como parte de una biblioteca paralela. Un tubo de reacción se cargó con etil 1-{3-[(terc-butoxicarbonil)amino] propil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (550 mg, 1.35 mmol) y ácido 4-metoxibencenobórico (307 mg, 2.02 mmol). La mezcla se purgó con N_2, y luego se agregaron 16 mL tolueno y 6 mL de una solución 2M de carbonato de sodio. La mezcla de reacción se purgó nuevamente con N_2. A esta mezcla en agitación se agregó [1,1'-bis(difenilfosfino) ferroceno]dicloropaladio II CH_2Cl_2 (88 mg, 0.11 mmol), y la reacción se calentó a 80°C durante 18 horas. Se decantó la capa acuosa, y la capa orgánica se filtró a través de celita, y se lavó con CH_2Cl_2. El filtrado se concentró *in vacuo, y* el residuo se trató con 10 mL de una solución 4 N de HCl en dioxano durante 1 hora. El producto se concentró *in vacuo*, se lavó con éter dietílico, y se secó por aire para proporcionar 673 mg (cuantitativo) del éster deseado. LCMS mostró un pico principal con m/z 381 (M+H).

[000306] Paso 2. Preparación de clorhidrato de ácido1-(3-aminopropil)-3-[2-(4-metoxifenil) piridin-4-il]-1H-pirazol-5-carboxílico.

[000307] Este compuesto se preparó como parte de una biblioteca paralela. Un tubo de reacción se cargó con clorhidrato de etil 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato (200 mg, 0.44 mmol) y 10 mL de una solución 2.5 N de NaOH. La mezcla se calentó a 100°C durante 30 minutos, y se concentró *in vacuo*. La mezcla del producto se cromatografió en una HPLC de fase reversa Gilson eluyendo con una gradiente de acetonitrilo/agua (5-70% CH_3CN durante 15 minutos). Las fracciones que contenían el producto deseado se combinaron y se concentraron. El aceite se absorbió en metanol y se trató con 5 mL de una solución 4 N de HCl en dioxano para obtener la sal HCl. La solución se concentró a sequedad, se lavó con éter dietílico, y se secó por aire para proporcionar 196 mg (cuantitativo) del ácido carboxílico del título. LCMS mostro un solo pico con m/z 353 (M+H). ES^+ HR MS calculado para M+H 353.1608, observado 353.1640.

EJEMPLO 72

[000308] Este ejemplo ilustra la producción de clorhidrato de ácido 1-(3-aminopropil)-3-{2-[4-(dimetilamino)fenil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000309] La preparación de clorhidrato de ácido 1-(3-aminopropil)-3-{2-[4-(dimetilamino)fenil]-piridin-4-il}-1H-pirazol-5-carboxílico se llevó a cabo en la misma manera que la descrita para la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico, usando ácido 4-dimetil(amino)fenilbórico. La purificación produjo el ácido carboxílico del título como un sólido anaranjado. Se obtuvo un rendimiento del 6% en 2 pasos. LCMS mostró un pico único con m/z 366 (M+H). ES^+ HR MS calculado para M+H 366.1925, observado 366.1918.

EJEMPLO 73

[000310] Este ejemplo ilustra la producción de clorhidrato de ácido 1-(3-aminopropil)-3-{2-[3-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000311] La preparación de clorhidrato de ácido 1-(3-aminopropil)-3-{2-[3-(hidroximetil) fenil]-piridin-4-il}-1H-pirazol-5-carboxílico se llevó a cabo en la misma manera que la descrita para la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico, usando ácido 3-hidroximetilfenilbórico. La purificación produjo el ácido carboxílico del título como un sólido café. Se obtuvo un rendimiento del 5% en 2 pasos. LCMS mostró un pico único con m/z 353 (M+H). ES^+ HR MS calculado para M+H 353.1608, observado 353.1608.

EJEMPLO 74

[000312] Este ejemplo ilustra la producción de clorhidrato de ácido 1-(3-aminopropil)-3-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000313] La preparación de clorhidrato de ácido 1-(3-aminopropil)-3-{2-[4-(trifluorometoxi)-fenil]piridin-4-il}-1H-pirazol-5-carboxílico se llevó a cabo en la misma manera que la descrita para la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico usando ácido 4-trifluorometoxi-bencenobórico. La purificación produjo el ácido carboxílico del título como un sólido café. Se obtuvo un rendimiento del 3% en 2 pasos. LCMS mostró un pico único con m/z 407 (M+H). ES^+ HR MS calculado para M+H 407.1326, observado 407.1358.

EJEMPLO 75

[000314] Este ejemplo ilustra la producción de 2-[2-(4-metoxifenil)-piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a] [1,4]diazepin-4-ona.

[000315] Este compuesto se preparó como parte de una biblioteca paralela. Un tubo de reacción se cargó clorhidrato de etil 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxilato (250 mg, 0.55 mmol), 20 mL de hidróxido de amonio, y 10 mL de etanol. La mezcla de reacción se agitó a la temperatura de la sala durante 18 horas. En seguida la mezcla se concentró *in vacuo*, se lavó con agua, se filtró, y se secó por vacío para proporcionar 150 mg (81 %) de la lactama del título como un sólido amarillento. LCMS mostró un pico único con m/z 335 (M+H). ^1H NMR (DMSO-d_6 + TFA/300 MHz) δ 8.78 (d, 1H), 8.68 (a, 1H), 8.43 (br s, 1H), 8.26 (d, 1H), 8.09 (d, 2H), 7.93 (s, 1H), 7.23 (d, 2H), 4.59 (m, 2H), 3.89 (s, 3H), 3.26 (m, 2H), 2.21 (m, 2H). ES^+ HR MS calculado para M+H 335.1503, observado 335.1490.

EJEMPLO 76

[000316] Este ejemplo ilustra la producción de trifluoroacetato de 2-{2-[4-(dimetilamino)-fenil]piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000317] La preparación trifluoroacetato de 2-{2-[4-(dimetilamino)fenil]piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-

a][1,4]diazepin-4-ona se llevó a cabo en una manera similar a la descrita para la preparación de 2-[2-(4-metoxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona, excepto que se cromatografió en una HPLC de fase reversa Gilson eluyendo con una gradiente de acetonitrilo/agua (5-70% CH_3CN durante 15 minutos). Las fracciones puras se combinaron y se concentraron para proporcionar la lactama del título como un sólido amarillo (44% rendimiento). LCMS mostró un pico único con m/z 348 (M+H). ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.61 (d, 1H), 8.52 (s, 1H), 8.41 (brs, 1H), 8.03 ((d, 2H), 7.98 (d, 1H), 7.84 (s, 1H), 6.89 (d, 2H), 4.57 (t, 2H), 3.25 (m, 2H), 3.05 (s, 6H), 2.21 (m, 2H). mp=223.0-226.7°C ES^+ HR MS calculado para M+H 348.1819, observado 348.1790.

EJEMPLO 77

[000318] Este ejemplo ilustra la producción de trifluoroacetato de 2-{2-[3-(hidroximetil)-fenil]piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000319] La preparación de trifluoroacetato de 2-{2-[3-(hidroximetil)fenil]piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona se llevó a cabo en una manera similar a la descrita para la preparación de 2-[2-(4-metoxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a] [1,4]diazepin-4-ona, excepto que se cromatografió en una HPLC de fase reversa Gilson eluyendo con una gradiente de acetonitrilo/agua (5-70% CH_3CN durante 15 minutos). Las fracciones puras se combinaron y se concentraron para proporcionar la lactama como un sólido blanco (26% rendimiento). LCMS mostró un pico único con m/z 335 (M+H). ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.71 (d, 1H), 8.40 (s, 1H), 8.35 (brs, 1H), 8.11 (s, 1H), 8.03 (d, 1H), 7.86 (d, 1H), 7.63 (s, 1H), 7.53-7.41 (m, 2H), 4.61 (s, 2H), 4.54 (t, 2H), 3.24 (m, 2H), 2.19 (m, 2H). ES^+ HR MS calculado para M+H 335.1503, observado 335.1520.

EJEMPLO 78

[000320] Este ejemplo ilustra la producción de 2-{2-[4-(trifluorometoxi)-

fenil]piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000321] La preparación de 2-{2-[4-(trifluorometoxi)fenil]piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona se llevó a cabo en una manera similar a la descrita parala preparación de 2-[2-(4-metoxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona. La mezcla se concentró enseguida *in vacuo*, se lavó con agua, se filtró, y se secó por vacío para proporcionar la lactama del título como un sólido blancuzco (65%). LCMS mostró un pico único con m/z 389 (M+H).

^{1}H nmr (DMSO-d_6 / 300 MHz) δ 8.70 (d, 1H), 8.40 (s, 1H), 8.33 (m, 3H), 7.82 (d, 1H), 7.62 (s, 1H), 7.49 (d, 2H), 4.53 (m, 2H), 3.24 (m, 2H), 2.19 (m, 2H). ES^+ HR MS calculado para M+H 389.1220, observado 389.1225.

EJEMPLO 79

[000322] Este ejemplo ilustra la producción de 2-{2-[4-(hidroximetil)fenil]piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000323] Paso 1. La preparación de clorhidrato de etil 1-(3-aminopropil)-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxilato se llevó a cabo en una manera similar a la descrita para la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico, Paso 1, usando ácido 4-hidroximetilfenilbórico. Al completarse la reacción, se agregaron acetato de etilo y agua. Las capas se separaron, y la capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo resultante se trató con exceso 4 N de HCl/dioxano durante 15 minutos a la temperatura de la sala. La mezcla de reacción se cromatografió entonces en una HPLC de fase reversa Gilson eluyendo con una gradiente de acetonitrilo/agua (5-70% CH_3CN durante 15 minutos). Las fracciones puras se combinaron, se absorbieron en MeOH, y se trataron con 4 N HCl/dioxano para proporcionar la sal HCl deléster de amina como un sólido rojo (19 % rendimiento). LCMS mostró un pico principal *m/z* 381 (M+H).

[000324] Paso 2. La preparación de 2-{2-[4-(hidroximetil)fenil] piridin-4-il}-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona se llevó a cabo en una manera similar a la descrita para la preparación de 2-[2-(4-metoxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a] [1,4]diazepin-4-ona. La mezcla del producto se concentró y se filtró para proporcionar la lactama como un sólido amarillento (44% rendimiento). LCMS mostró un pico único con m/z 335 (M+H). ES^+ HR MS calculado para M+H 335.1503, observado 335.1520.

EJEMPLO 80

[000325] Este ejemplo ilustra la producción de clorhidrato de etil 1-(3-aminopropil)-3-[2-(4-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000326] La preparación de clorhidrato de etil 1-(3-aminopropil)-3-[2-(4-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxilato se llevó a cabo en una manera similar a la descrita para la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico, Paso 1, usando éter THP de ácido 4-hidroxifenilbórico. Al completarse la reacción en Paso 1, se agregaron acetato de etilo y agua. Las capas se separaron, y la capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se trató con exceso 4 N HCl/dioxano durante 15 minutos. La mezcla se concentró, se trituró con éter, y se filtró para proporcionar el éster de la amina del título como un sólido amarillento (95% rendimiento). LCMS mostró un pico principal m/z 367 (M+H). m.p. = 241.6-244.4 °C.

EJEMPLO 81

[000327] Este ejemplo ilustra la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxílico.

[000328] La preparación de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-hidroxifenil) piridin-4-il]-1H-pirazol-5-carboxílico se llevó a cabo en una manera similar a la descrita para la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)-piridin-4-il]-1H-pirazol-5-carboxílico,

Paso 2. El ácido carboxílico del título se obtuvo como un sólido blancuzco (51% rendimiento). LCMS mostró un pico único con m/z 339 (M+H). ES^+ HR MS calculado para M+H 339.1452, observado 339.1455.

EJEMPLO 82

[000329] Este ejemplo ilustra la producción de trifluoroacetato de 2-[2-(4-hidroxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona.

[000330] La preparación de trifluoroacetato de 2-[2-(4-hidroxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4]diazepin-4-ona se llevó a cabo en una manera similar a la descrita parala preparación de 2-[2-(4-metoxifenil)piridin-4-il]-5,6,7,8-tetrahidro-4H-pirazolo[1,5-a][1,4] diazepin-4-ona. Al completarse la reacción, la mezcla del producto se concentró, se lavó con agua, y se filtró. La mezcla se cromatografió entonces en una HPLC de fase reversa Gilson eluyendo con una gradiente de acetonitrilo/agua (5-70% CH_3CN durante 15 minutos). Las fracciones puras se combinaron y se concentraron para proporcionar el compuesto del título como un sólido blancuzco (41% rendimiento). LCMS mostró un pico único con m/z 321 (M+H). ^1H NMR (DMSO-d_6 / 300 MHz) δ 8.72 (d, 1H), 8.63 (s, 1H), 8.42 (br s, 1H), 8.22 (d, 1H), 8.02 (d, 2H), 7.81 (s, 1H), 7.03 (d, 2H), 4.57 (m, 2H), 3.25 (m, 2H), 2.20 (m, 2H). ES^+ HR MS calculado para M+H 321.1346, observado 321.1368.

EJEMPLO 83

[000331] Este ejemplo ilustra la producción de trifluoroacetato de ácido 1-(3-{[2-(4-bromofenil)etil]-amino}propil)-3-{2-[(E)-2-fenilvinil]piridin-4-il}-1H-pirazol-5-carboxílico.

[000332] Paso 1. Preparación de etil 1-{3-[[2-(4-bromofenil)etil](terc-butoxicarbonil)-amino]propil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato. Un matraz de fondo redondo de un solo cuello se cargó con etil 3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (1.0 g, 4.0 mmol) y 30 mL de dimetil formamida bajo N_2. La solución se enfrió a -40 °C en un

baño de hielo seco / acetonitrilo. Se agregó gota a gota una solución 1 M de *t*-butóxido de litio en THF (4.8 mL, 4.8 mmol) durante 5 minutos. La reacción se agitó durante 1 hora a -40 °C. Se agregó gota a gota durante 5 minutos una solución de 3-[[2-(4-bromofenil)etil](terc-butoxicarbonil)amino]propilmetanosulfonato (2.1 g, 4.8 mmol) en 10 mL dimetilformamida. La mezcla de reacción resultante se agitó durante 1 hora a -40 °C, y en seguida se agitó durante 18 horas a la temperatura de la sala. La mezcla se concentró entonces, y el residuo se absorbió en éter dietílico. Las impurezas sólidas se extrajeron por filtración, y se lavaron con éter dietílico. El filtrado se concentró en un aceite café. LCMS mostró una mezcla del éster etílico y el ácido carboxílico hidrolizado. Esta mezcla del producto se tomó en el Paso siguiente sin purificación posterior.

[000333] Paso 2. La preparación de clorhidrato de etil 1-(3-{[2-(4-bromofenil)etil]amino}-propil)-3-{2-[(E)-2-fenilvinil]piridin-4-il}-1H-pirazol-5-carboxilato se llevó a cabo en una manera similar a la descrita en Ejemplo 2, Paso 1, usando ácido 2-fenilvinilbórico. Al completarse la reacción, se agregaron acetato de etilo y agua. Las capas se separaron, y la capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se trató con exceso 4N HCl/dioxano durante 30 minutos. La mezcla se concentró, se lavó con éter, y se filtró para proporcionar el éter etílico como un sólido café (29% rendimiento en 2 pasos). LCMS mostró un pico principal m/z 559 (M+H). ES^+ HR MS calculado para M+H 559.1703, observado 559.1679.

[000334] Paso 3. La preparación de trifluoroacetato de ácido 1-(3-{[2-(4-bromofenil)etil]amino}propil)-3-{2-[(E)-2-fenilvinil]piridin-4-il}-1H-pirazol-5-carboxílico se llevó a cabo en una manera similar a la descrita para la producción de clorhidrato de ácido 1-(3-aminopropil)-3-[2-(4-metoxifenil)piridin-4-il]-1H-pirazol-5-carboxílico, Paso 2. Al completarse la reacción, la mezcla se concentró. El residuo se cromatografió entonces en una HPLC de fase reversa Gilson eluyendo con una gradiente de acetonitrilo/agua (5-70% CH_3CN durante 15 minutos). Las fracciones puras se combinaron y se concentraron para proporcionar el compuesto del

título como un sólido blancuzco (30% rendimiento). LCMS mostró un pico único con m/z 531 (M+H). ES^+ HR MS calculado para M+H 531.1390, observado 531.1411.

EJEMPLO 84

[000335] Este ejemplo ilustra la producción de etil 1-{2-[(terc-butoxi-carbonil)amino]etil}-3-[2-(4-{[terc-butil(dimetil)silil]oxi}fenil)-piridin-4-il]-1H-pirazol-5-carboxilato.

[000336] Etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-1H-pirazol-5-carboxilato (5.0 g, 0.013 mol), ácido 4-(t-butildimetilsililoxi)fenilbórico (6.4 g, 0.025 mol), carbonato de sodio (2.7 g, 0.025 mol), agua (12.5 mL), y complejo de [1,1'-bis (difenilfosfino)ferroceno]dicloropaladio (II) con diclorometano (1:1) (1.0 g, 0.0013 mol) en tolueno (100 mL) se hicieron refluir durante 4 horas. Se dejaron enfriar los contenidos y de repartieron en porciones entre EtOAc y agua. La capa EtOAc se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró *in vacuo*. El residuo se filtró a través de una almohadilla de gel de sílice, eluyendo con 25% EtOAc/hexanos para producir un aceite color ámbar claro. El aceite se cristalizó bajo hexanos y se filtró para producir el producto deseado como un sólido blanco, 3.77 g (51% rendimiento). FABHRMS m/z 567.2983 (M+H, $C_{30}H_{43}N_4O_5Si$ requiere 567.2997). ^1H NMR ($CDCl_3$ / 300 MHz): 8.70 (s, 1H); 8.12 (s, 1H); 7.97 (d, 2H); 7.60 (s, 1H); 7.29 (d, 1H); 6.95 (d, 2H); 4.97 (br, 1H); 4.77 (t, 2H); 4.40 (q, 2H); 3.63 (br, 2H); 1.40 (t, 3H); 1.38 (s, 9H); 1.00 (s, 9H); 0.25 (s, 6H).

[000337] Análisis calculado para $C_{30}H_{42}N_4O_5Si$: C, 63.58; H, 7.47; N, 9.89. Hallado: C, 63.51; H, 7.58; N, 9.73.

EJEMPLO 85

[000338] Este ejemplo ilustra la preparación de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(4-{[terc-butil(dimetil)silil]oxi}fenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000339] Etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-[2-(4-{[terc-

butil(dimetil)-silil]oxi}fenil)piridin-4-il]-1H-pirazol-5-carboxilato (1.0 g, 0.0018 mol) y 4N HCl en dioxano se mezclaron durante 2 horas y se filtraron para producir el producto deseado como un sólido blanco, 875 mg (90% rendimiento). FABHRMS m/z 467.2450 (M+H, $C_{25}H_{35}N_4O_3Si$ requiere 467.2473). ^1H NMR (DMSO-d_6 + TFA/300 MHz): 8.80 (d, 1H); 8.75 (s, 1H); 8.35 (d, 1H); 8.22 (br, 3H); 8.20-8.10 (m, 3H); 7.13 (d, 2H); 4.90 (t, 2H); 4.40 (q, 2H); 3.40 (q, 2H); 1.39 (t, 3H); 0.95 (s, 9H); 0.23 (s, 6H).

[000340] Análisis calculado para $C_{25}H_{34}N_4O_3Si$ (2 HCl, 1.1 H_2O): C, 53.68; H, 6.88; N, 10.02. Hallado: C, 53.34; H, 6.98; N, 10.18.

EJEMPLO 86

[000341] Este ejemplo ilustra la producción de 2-[2-(4-hidroxifenil) piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000342] Diclorhidrato de etil 1-(2-aminoetil)-3-[2-(4-{[terc-butil(dimetil)silil]oxi} fenil)piridin-4-il]-1H-pirazol-5-carboxilato (770 mg, 0.0014 mol), hidróxido de amonio concentrado (2 mL) y metanol (20 mL) se agitaron de un día para otro. Los contenidos se concentraron *in vacuo* y el residuo se suspendió en agua y se filtró para producir el producto deseado como un sólido blanco, 373 mg, (87% rendimiento). FABHRMS m/z 307.1222 (M+H, $C_{17}H_{15}N_4O_2$ requiere 307.1190). ^1H NMR (DMSO-d_6 + TFA/300 MHz): 8.75 (d, 1H); 8.63 (s, 1H); 8.40 (s, 1H); 8.21 (d, 1H); 8.00-7.95 (m, 3H); 7.00 (d, 2H); 4.43 (t, 2H); 3.65 (br, 2H).

[000343] Análisis calculado para $C_{17}H_{14}N_4O_2$ (1.3 H_2O): C, 61.92; H, 5.07; N, 16.99. Hallado: C, 61.79; H, 5.11; N, 16.85.

EJEMPLO 87

[000344] Este ejemplo ilustra la producción de 2-{2-[4-(2-morfolin-4-iletoxi)fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000345] 2-[2-(4-hidroxifenil)piridin-4-il]-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona (500 mg, 0.0016 mol), clorhidrato de 4-(2-cloroetil)morfolina (372 mg (0.002 mol) y carbonato de potasio (600 mg,

0.004 mol) se calentaron en DMF (20 mL) a 80°C durante 3 horas. Se dejaron enfriar los contenidos, se diluyeron con agua (50 mL), se enfriaron a 0°C y se filtraron para producir el producto deseado como un sólido blanco, 515 mg (77% rendimiento). FABHRMS m/z 420.2004 (M+H, $C_{23}H_{26}N_5O_3$ requiere 420.2030). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.81 (d, 1H); 8.66 (s, 1H); 8.43 (s, 1H); 8.23 (d, 1H); 8.15 (d, 2H); 7.94 (s, 1H); 7.28 (d, 2H); 4.55-4.40 (m, 4H); 4.05-3.95 (m, 2H); 3.80-3.50 (m, 8H); 3.30-3.18 (m, 2H).

[000346] Análisis calculado para $C_{23}H_{25}N_5O_3$ (0.8 H_2O): C, 63.60; H, 5.96; N, 16.25. Hallado: C, 63.67; H, 6.18; N, 16.14.

EJEMPLO 88

[000347] Este ejemplo ilustra la producción de 2-(2-{4-[2-(dimetilamino)etoxi]-fenil}piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000348] 2-(2-{4-[2-(dimetilamino)etoxi]fenil}piridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona se preparó de acuerdo con el procedimiento de 2-{2-[4-(2-morfolin-4-iletoxi)fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona para producir el producto deseado como un sólido blanco (72% rendimiento). FABHRMS m/z 378.1901 (M+H, $C_{21}H_{24}N_5O_2$ requiere 378.1925). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 9.80 (br, 1H); 8.80 (d, 1H); 8.70 (s, 1H); 8.42 (s, 1H); 8.28 (d of d, 1H); 8.12 (d, 2H); 7.96 (s, 1H); 7.28 (d, 2H); 4.50-4.40 (m, 4H); 3.70 (br, 2H); 3.60 (br, 2H); 2.90 (s, 6H). Análisis calculado para $C_{21}H_{23}N_5O_2$ (0.6 H_2O): C, 64.91; H, 6.15; N, 18.03. Hallado: C, 64.97; H, 6.28; N, 18.04.

EJEMPLO 89

[000349] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-{2-[3-(benciloxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato.

[000350] Etil 1-{2-[(terc-butoxicarbonil)amino]etil}-3-(2-cloropiridin-4-il)-

1H-pirazol-5-carboxilato y ácido 3-benciloxibórico se hicieron reaccionar de acuerdo con el procedimiento descrito para la preparación de etil 1-{2-[(terc-butoxicarbonil)-amino]etil}-3-[2-(4-{[terc-butil (dimetil)silil]oxi}fenil)piridin-4-il]-1H-pirazol-5-carboxilato, para producir etil 1-(2-t-butoxicarbonilaminoetil)-3-{2-[3-(benciloxi-fenil]piridin-4-il}-1H-pirazol-5-carboxilato como un aceite color ámbar claro. Etil 1-(2-t-butoxicarbonilaminoetil)-3-{2-[3-(benciloxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato y 4N HCl en dioxano se agitaron 3 horas y se filtraron para producir el producto deseado como un sólido amarillo pálido, 8.0 g (81% rendimiento). FABHRMS m/z 443.2053 (M+H, $C_{26}H_{27}N_4O_3$ requiere 443.2078). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.88 (d, 1H); 8.80 (s, 1H); 8.10 (s, 1H); 8.05 (br, 3H); 7.78 (s, 1H); 7.65 (d, 1H); 7.55 (t, 1H); 7.45 (d, 1H); 7.40-7.30 (m, 6H); 5.21 (s, 2H); 4.85 (t, 2H); 4.35 (q, 2H); 3.40 (q, 2H); 1.35 (t,3H).

[000351] Análisis calculado para $C_{23}H_{26}N_4O_3$ (3HCl, H_2O): C, 54.80; H, 5.48; N, 9.83. Hallado: C, 55.01; H, 5.84; N, 10.75.

EJEMPLO 90

[000352] Este ejemplo ilustra la producción de 2-{2-[3-(benciloxi) fenil]-piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000353] 2-{2-[3-(benciloxi)fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona se preparó de acuerdo con el procedimiento para la preparación de 2-[2-(4-hidroxifenil)piridin-4-il]-6,7-dihidropirazolo [1,5-a]pirazin-4(5H)-ona, usando diclorhidrato de etil 1-(2-aminoetil)-3-{2-[3-(benciloxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato, para producir el producto deseado como un sólido blanco (63% rendimiento). FABHRMS m/z 397.1634 (M+H, $C_{24}H_{21}N_4O_2$ requiere 397.1659). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.81 (d, 1H); 8.62 (s, 1H); 8.40 (s, 1H); 8.21 (d, 1H); 7.92 (s, 1H); 7.80 (s, 1H); 7.70 (d, 1H); 7.63 - 7.25 (m, 6H); 5.23 (s, 2H); 4.51-4.40 (m, 2H); 3.78-3.60 (m, 2H). Análisis calculado para $C_{24}H_{20}N_4O_2$ (H_2O): C, 69.55; H, 5.35; N, 13.52. Hallado: C, 69.65; H, 5.11; N, 14.50.

EJEMPLO 91

[000354] Este ejemplo ilustra la producción de diclorhidrato de etil 1-(2-aminoetil)-3-[2-(3-hidroxifenil)piridin-4-il]-1H-pirazol-5-carboxilato.

[000355] Etil 1-(2-t-butoxicarbonilaminoetil)-3-{2-[3-(benciloxi)fenil] piridin-4-il}-1H-pirazol-5-carboxilato (9.1 g, 0.017 mol), preparado como para diclorhidrato de etil 1-(2-aminoetil)-3-{2-[3-(benciloxi)fenil]piridin-4-il}-1H-pirazol-5-carboxilato y 10% paladio/carbón (2.0 g) en etanol (150 mL) se agitaron a 55 psi H_2 en un hidrogenador Parr durante tres días y medio. Los contenidos se filtraron a través de arcilla y el filtrado se concentró *in vacuo* dejando un sólido amarillo pálido (6.4 g). El sólido y 4N HCl en dioxano se agitaron de un día para otro y se filtraron para producir el producto deseado como un sólido blanco, 6.0 g (83% rendimiento). HRMS calculado para (M + H) 353.1608, hallado 353.1630. ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.86 (d, 1H); 8.77 (s, 1H); 8.40 (d, 1H); 8.20 (br s, 3H); 8.12 (s, 1H); 7.59-7.40 (m, 3H); 7.09 (d, 1H); 4.90 (t, 2H), 4.39 (q, 2H); 3.40 (q, 2H); 1.35 (t, 3H).

EJEMPLO 92

[000356] Este ejemplo ilustra la producción de 2-{2-[3-(2-morfolin-4-iletoxi)-fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona.

[000357] 2-{2-[3-(2-morfolin-4-iletoxi)fenil]piridin-4-il}-6,7-dihidropirazolo-[1,5-a]pirazin-4(5H)-ona se preparó de acuerdo con el procedimiento para 2-{2-[4-(2-morfolin-4-iletoxi)fenil]piridin-4-il}-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona, usando 2-[2-(3-hidroxifenil) piridin-4-il]-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona y clorhidrato de cloroetilmorfolina para producir el compuesto deseado como un sólido blanco (55% rendimiento). FABHRMS m/z 420.1996 (M+H, $C_{23}H_{26}N_5O_3$ requiere 420.2030). ^{1}H NMR (DMSO-d_6 + TFA/300 MHz): 8.85 (d, 1H); 8.61 (s, 1H); 8.40 (s, 1H); 8.21 (d, 1H); 7.89 (s, 1H); 7.78 (s, 2H);7.59 (t, 1H); 7.28 (d, 1H); 4.58-4.40 (m, 4H); 4.08-3.91 (m 2H); 3.84-3.48 (m, 8H); 3.45-3.13 (m, 2H).

[000358] Análisis calculado para $C_{23}H_{25}N_5O_3$ (0.7 H_2O): C, 63.93; H, 6.16; N, 16.21. Hallado: C, 63.93; H, 5.96; N, 16.42.

EJEMPLO 93

[000359] Este ejemplo ilustra la preparación de 2-(2-Cloropiridin-4-il)-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c]piridin-4-ona.

[000360] Paso 1. Preparación de clorhidrato de 2-cloro-4-hidrazinopiridina. Una solución de 4-amino-2-cloropiridina (1.0 g, 7.78 mmol) en ácido sulfúrico al 20% (20 mL) se enfrió a 0°C y se trató con una solución de nitrito de sodio (564 mg, 8.17 mmol) en agua (3 mL) a un ritmo tal que la temperatura de reacción no excediera 10°C. Después de 15 minutos, la solución se agregó una suspensión a 0°C de cloruro de estaño (II) en ácido sulfúrico al 20% (20 mL). La suspensión espumosa se agitó durante 15 minutos a 0 °C y luego se calentó a la temperatura de la sala durante 15 minutos. La mezcla se vertió en 100 mL de agua helada y se hizo alcalina con hidróxido de amonio concentrado. El producto se extrajo con éter dietílico y acetato de etilo repetidamente. Las capas orgánicas se secaron (sulfato de sodio) y se concentraron para producir 2-cloro-4-hidrazinopiridina cruda como un sólido amarillo (830 mg, 5.78 mmol). El sólido se disolvió en tetrahidrofurano (5 mL) y se diluyó con éter dietílico (15 mL). La solución se trató con 1 N HCl en éter dietílico (5.8 mL, 5.8 mmol). El precipitado blanco se filtró y se lavó con éter para producir clorhidrato de 2-cloro-4-hidrazinopiridina como un sólido blanco (995 mg, 5.53 mmol, 71% rendimiento). LC-MS (ES+) MH^+ = 144. ^1H NMR (300 MHz, DMSO-d_6) δ 10.0-9.40 (br s, 4H), 8.07 (d, J = 6.1, 1H), 6.95 (d, J = 1.9,1H), 6.86 (dd, J = 5.8, 2.0,1H).

[000361] Paso 2. Preparación de Piperidin-2,4-diona 4-[(2-cloropiridin-4-il)hidrazona]. Una mezcla de clorhidrato de 2-cloro-4-hidrazinopiridina (961 mg, 5.33 mmol), piperdien-2.4-diona (Ejemplo 1, paso 3) (604 mg, 5.33 mmol) y etanol (20 mL) se hizo refluir de un día para otro. La mezcla de reacción se enfrió a la temperatura de la sala, se diluyó con éter dietílico (20 mL), y se filtró. El precipitado se lavó con 50% etanol/éter dietílico y

se secó para producir piperidin-2,4-diona 4-[(2-cloropiridin-4-il)hidrazona] como un sólido blancuzco (940 mg, 3.94 mmol, 74% rendimiento). LC-MS (ES+) $MH^+ = 239$.

[000362] Paso 3. Preparación de 2-(2-Cloropiridin-4-il)-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c]piridin-4-ona.

[000363] Una mezcla de piperidin-2,4-diona 4-[(2-cloropiridin-4-il) hidrazona] (863 mg, 3.62 mmol) en dimetil acetal de dimetilformamida (16 mL) se hizo refluir durante 1 hora. El disolvente se retiró bajo presión reducada. El residuo se suspendió en etanol/éter dietílico y se filtró. El precipitado se lavó con 50% etanol/éter dietílico para producir 2-(2-cloropiridin-4-il)-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c]piridin-4-ona como un sólido blancuzco (378 mg, 1.52 mmol, 42% rendimiento). El agua madre se concentró y se purificó por cromatografía de destello (0→10% metanol/acetato de etilo). El aceite resultante se trituró con metanol/éter para producir otros 58 mg (0.23 mmol, 6%) de 2-(2-cloropiridin-4-il)-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c]piridin-4-ona. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.47 (d, J = 5.7, 1H), 8.04 (d, J = 1.6,1H), 7.94 (dd, J = 5.5, 1.8, 1H), 7.71 (br s, 1H), 3.44 (td, J = 6.5, 2.6, 2H), 2.89 (t, J = 6.6, 2H). HRMS calculado para $C_{11}H_{10}ClN_4O$ (MH^+) 249.0538, hallado 249.0545.

EJEMPLO 94

[000364] Este ejemplo ilustra la preparación de bis(trifluoroacetato) de 2-(2-quinolin-3-ilpiridin-4-il)-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c]piridin-4-ona.

[000365] El compuesto del título se preparó de 2-(2-cloropiridin-4-il)-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c]piridin-4-ona (Ejemplo 508) y ácido 3-quinolinilbórico por el procedimiento descrito para Ejemplo 2. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (d, J = 2.2, 1H), 9.38 (s, 1H), 9.26 (d, J = 2.0, 1H), 8.82 (d, J = 5.4, 1H), 8.71 (d, J = 1.6, 1H), 8.16 (d, J =7.7, 1H), 8.12 (d, J = 8.3, 1H), 7.96 (dd, J = 5.6, 2.0, 1H), 7.87 (td, J = 7.7, 1.3,1H), 7.76-7.68 (m, 2H), 3.48 (td, J = 6.6, 2.4, 2H), 2.95 (t, J = 6.6, 2H). HRMS

calculado para $C_{20}H_{16}N_5O$ (MH^+) 342.1349, hallado 342.1334.

[000366] Los siguientes ejemplos se elaboraron por el mismo método.

Ejemplo No.	Nombre (s) del Compuesto	Calculado (m+H)	Hallado (m+H)
95	Trifluoroacetato de 2-[2-(2-fluorofenil)piridin-4-il]-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c]piridin-4-ona	309.1146	309.119
96	Trifluoroacetato de 2-(2-fenilpiridin-4-il)-2,5,6,7-tetrahidro-4H-pirazolo[4,3-c] piridin-4-ona	291.124	291.1252

EJEMPLO 97

[000367] Este ejemplo ilustra la preparación de trifluoroacetato de 2-{2-[(E)-2-(4-morfolin-4-ilfenil)vinil]piridin-4-il}-6,7-dihidropirazolo[1,5-a] pirazin-4(5H)-ona.

[000368] mp 290°C (descomposición); ^{1}H NMR (300 MHz, DMSO-d_6) 58.62 (d, J= 6.5 Hz, 1H), 8.39 (2 x s, 2H), 7.97-7.83 (m, 2H), 7.70 (s, 1H), 7.57 (d, *J*= 8.6 Hz, 2H), 7.15 (d, J= 16.2 Hz, 1H), 7.03 (d, J= 16.2 Hz, 2H), 4.50-4.38 (m, 2H), 3.80-3.60 (m, 6H), 3.28-3.19 (m, 4H); *m/z* 402 $[M+H]^+$

EJEMPLO 98

[000369] Este ejemplo ilustra que ratones con deficiencia genética del transportador de dopamina MK2 (*"knock-out mice"*) (MK2 (-/-)) son resistentes a la formación de artritis inducida por suero K/BN y que compuestos que inhiben MK-2 deben ser efectivos para la prevención y tratamiento de enfermedades y trastornos mediados por TNFα.

Se ha informado de un linaje de ratones que desarrolla síntomas similares a la artritis reumatoide humana. Los ratones se designaron ratones K/BxN. Véase, Wipke, B. T. and P. M. Allen, *J. of Immunology, 167*:1601 -1608 (2001). Suero de los ratones puede inyectarse en animales anfitriones para provocar una respuesta RA típica. La evolución de los síntomas RA en

los ratones se determina midiendo el espesor de la garra como función del tiempo.

[000370] En el presente ejemplo, ratones anfitriones con una producción normal de MK-2 (MK2 (+/+)) se alteraron genéticamente reactivando el gen que codifica MK-2 para producir ratones sin capacidad de síntesis endógena de MK-2 activa (MK2 (-/-)). Ratones anfitriones normales (MK2 (+/+)) y ratones con deficiencia de MK-2 (MK2 (-/-), se separaron en cuatro grupos, conteniendo cada grupo ratones masculinos y femeninos. Todos los grupos de ratones se trataron en forma similar, excepto que un grupo (Normal), compuesto de ratones MK2 (+/+), que sirvieron como el grupo de control, no se inyectó con suero de ratones K/BxN, mientras los otros tres grupos se inyectaron con suero K/BxN el día 0. Los otros tres grupos de ratones fueron MK2 (+/+), MK2 (-/-), y Anti-TNF. El grupo Anti-TNF estaba compuesto de ratones MK2 (+/+), los cuales se inyectaron también el día 0 con anticuerpo anti-TNF. El espesor de la garra de todos los ratones se midió inmediatamente después de las inyecciones el día 0, y luego en cada día sucesivo a partir de ahí durante 7 días.

[000371] Figura 1 es un gráfico que muestra el espesor de la garra como función del tiempo del día 0 al día 7 para ratones MK2 (+/+) y MK2 (-/-), que habían recibido inyección de suero. Puede observarse que el espesor de la garra aumentó significativamente para los ratones MK2(+/+), mientras que no hubo sustancialmente incremento en el espesor de la garra para ratones con deficiencia de MK2. Esto indicó el requerimiento de un sistema regulador de MK2 en funcionamiento a la respuesta inflamatoria causada por la prueba de provocación con suero (***"serum challenge"***) Cuando se administró anticuerpo anti-TNF a los ratones MK2 (+/+) junto con la inyección de suero, se redujo significativamente la respuesta de hinchazón. Esto puede observarse en Figura 2, que es un cuadro de barras que muestra el espesor de la garra siete días después de la inyección para ratones normales, ratones MK2 (+/+) que recibieron suero, ratones MK2 (-/-) que recibieron suero, y ratones MK2 (+/+) que recibieron suero y anticuerpo anti-TNF.

[000372] Estos datos señalan que los ratones con deficiencia de MK-2 ("*MK2 knock-out mice*") no muestran respuesta artrítica a la prueba de provocación con suero, mientras que los ratones MK2 (+/+) muestran una respuesta normal. El tratamiento de ratones MK2 (+/+) que recibieron una prueba de provocación con suero con anticuerpo anti-TNF reduce la respuesta a niveles cercanos a los normales. Esto ilustra la utilidad del sistema regulador de MK2 como un punto de control potencial para la modulación de la producción de TNF, e indica que tal regulación podría servir como un tratamiento de la inflamación – tal como la causada por artritis, por ejemplo. Muestra asimismo que la inhibición de MK2 puede tener un efecto benéfico sobre la inflamación, e indica que la administración de un inhibidor de MK2 puede ser un método efectivo de prevenir o tratar enfermedades o tastornos mediados por TNF.

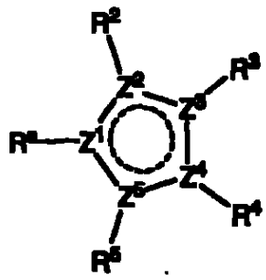
[000373] Todas las referencias citadas en esta especificación, incluyendo sin limitación todos los documentos, publicaciones, patentes, solicitudes de patente, presentaciones, textos, informes, manuscritos, folletos, libros, mensajes a grupos de discusión en internet ("*internet postings*") , artículos periodísticos, periódicos, y similares, se incorporan aquí por referencia en esta especificación en su totalidad. La discusión de las referencias contenidas aquí sólo tiene como finalidad compilar las afirmaciones hechas por sus autores y no implica la admisión de que cualquier referencia constituye arte previo. Los solicitantes se reservan el derecho de cuestionar la exactitud y pertinencia de las referencias citadas.

[000374] En vista de lo anterior, se observará que se logran varias ventajas de la invención y se obtienen otros resultados.

[000375] Como pueden hacerse diferentes modificaciones en los métodos y composiciones anteriores sin apartarse del ámbito de la invención, se tiene la intención que toda la materia contenida en la anterior descripción se interpretará como ilustrativa y no en un sentido limitante.

LO QUE SE REIVINDICA ES:

1. Un compuesto que tiene la estructura

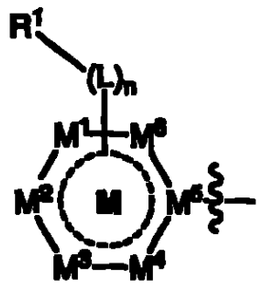


en donde:

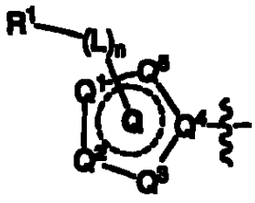
Z^2 y Z^3 son nitrógeno, Z^1, Z^4 y Z^5 son carbono, y se juntan con Z^2 y Z^3 para formar un anillo pirazol, o de manera opcional, Z^4 y Z^5 son nitrógeno, Z^1, Z^2 y Z^3 son carbono y se juntan con Z^4 y Z^5 para formar un anillo pirazol;

R^a se selecciona de:

1)



2)



, y

3)



donde las líneas discontinuas indican enlaces simples o dobles

opcionales;

cuando R^a es anillo M y anillo M es aromático, M^1 es carbono y es sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono y nitrógeno y es no sustituido o sustituido con $(L)_nR^1$;

cuando anillo M es parcialmente saturado, M^1 es carbono y es mono- o di-sustituido con $(L)_nR^1$, M^5 es carbono, y cada uno de M^2, M^3, M^4 y M^6 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y cuando M^2, M^3, M^4, o M^6 es oxígeno o azufre, es no sustituido, y cuando M^2, M^3, M^4 o M^6 es carbono o nitrógeno, es opcionalmente no sustituido; o mono- o di-sustituido con $(L)_nR^1$;

cuando R^a es anillo Q y anillo Q es aromático, Q^1 se selecciona de carbono y nitrógeno, y cuando Q^1 es carbono, se sustituye con $(L)_nR^1$, y cuando Q^1 es nitrógeno, es no sustituido, Q^4 se selecciona de nitrógeno y carbono, y cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

opcionalmente, cuando anillo Q es aromático, Q^1 es carbono y es sustituido con $(L)_nR^1$, Q^4 es carbono, y uno de Q^2, Q^3 y Q^5 es opcionalmente oxígeno o azufre, y el resto de Q^2, Q^3 y Q^5 se seleccionan independientemente de nitrógeno y carbono, y si carbono, se sustituyen con $(L)_nR^1$;

cuando anillo Q es parcialmente saturado, Q^1 se selecciona de carbono y nitrógeno, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$, Q^4 se selecciona de carbono y nitrógeno, pero sólo uno de Q^1 y Q^4 puede ser nitrógeno, cada uno de Q^2, Q^3 y Q^5 se selecciona independientemente de carbono, nitrógeno, oxígeno y azufre, y si oxígeno o azufre, es no sustituido, y si carbono, es mono- o disustituido con $(L)_nR^1$, y si nitrógeno, es no sustituido o sustituido con $(L)_nR^1$;

cuando R^a es estructura 3, es completamente conjugado, X^2 se selecciona de oxígeno o nitrógeno sustituido con $(L)_nR^1$, X^1 es carbono y es sustituido con $(L)_nR^1$, y cada uno de X^5 y X^6 se selecciona

independientemente de nitrógeno y carbono, y si carbono, se sustituye con $(L)_nR^1$;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-R^{11}, C_2-C_6 alquenil-R^{11}, C_2-C_6 alquinil-R^{11}, C_1-C_6 alquil-$(R^{11})_2$, C_2-C_6 alquenil-$(R^{11})_2$, CSR^{11}, amino, $CONHR^{11}$, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NR^8R^9, $(C_1$-$C_4)$alquil-$N(R^7)$-$N(R^8)(R^9)$, $(C_1$-$C_4)$alquil$C(R^{11})$=N-$N(R^8)(R^9)$, $(C_1$-$C_4)$alquil-N=$N(R^7)$, $(C_1$-$C_4)$alquil-$N(R^7)$-N=$C(R^8)$, nitro, ciano, CO_2R^{11}, O-R^{10}, C_1-C_4 alquil-OR^{10}, COR^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_6 alquil-COR^{11}, C_1-C_6 alquil-SR^{10}, C_1-C_6 alquil-SOR^{11}, C_1-C_6 alquil-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{12};

R^7, R^8 y R^9 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alquil-OR^{15}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, $C(O)R^{17}$, $C(S)R^{17}$, $CONHR^{16}$, $C(S)NHR^{16}$, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SR^{15}, SOR^{17}, SO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de

manera opcional por uno o más de los grupos definidos por R^{18};

R^{10} se selecciona de -H, C_1-C_{10} alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, C_1-C_4 alquil-OR^{15}, CSR^{11}, CO_2R^{15}, $C(S)OR^{15}$, $C(O)SR^{15}$, COR^{17}, $C(S)R^{17}$, $CONHR^{16}$, C_1-C_4 alquil-R^{11}, C_1-C_4 alquil-NH_2R^{13}, $C(S)NHR^{16}$, O-R^{15}, $CON(R^{16})_2$, $C(S)N(R^{16})_2$, SOR^{17}, SO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, $Si(R^{13})_2R^{17}$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_2-C_6 alquenilo, C_2-C_6 alquinilo, amino, NHR^{13}, $NR^{13}R^{14}$, $N{=}NR^{13}$, C_1-C_6 alquil-NHR^{13}, C_1-C_6 alquil-$NR^{13}R^{14}$, O-R^{15}, C_1-C_4 alquil-OR^{15}, SR^{15}, COR^{13}, CO_2R^{17}, C_1-C_6 alquil-CO_2R^{15}, C_1-C_6 alquil-$C(S)OR^{15}$, C_1-C_6 alquil-$C(O)SR^{15}$, C_1-C_6 alquil-COR^{17}, C_1-C_6 alquil-$C(S)R^{17}$, C_1-C_6 alquil-$CONHR^{16}$, C_1-C_6 alquil-$C(S)NHR^{16}$, C_1-C_6 alquil-$CON(R^{16})_2$, C_1-C_6 alquil-$C(S)N(R^{16})_2$, C_1-C_6 alquil-SR^{15}, C_1-C_6 alquil-SOR^{17}, C_1-C_6 alquil-SO_2R^{17}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, OH, oxo, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{11}, C_2-C_{10} alquenil-R^{11}, C_2-C_{10} alquinil-R^{11}, C_1-

C_{10} alquil-$(R^{11})_2$, C_2-C_{10} alquenil-$(R^{11})_2$, CSR^{11}, hidroxil C_1-C_6 alquil-R^{11}, amino C_1-C_4 alquil-R^7, amino, NHR^7, NR^8R^9, $N(R^7)$-$N(R^8)(R^9)$, $C(R^{11})$=N-$N(R^8)(R^9)$, N=$N(R^7)$, $N(R^7)$-N=$C(R^8)$, $C(R^{11})$=N-$O(R^{10})$, ON=$C(R^{11})$, C_1-C_{10} alquil-NHR^7, C_1-C_{10} alquil-NR^8R^9, (C_1-C_{10})alquil-$N(R^7)$-$N(R^8)(R^9)$, (C_1-C_{10})alquil$C(R^{11})$=N-$N(R^8)(R^9)$,(C_1-C_{10})alquil-N=$N(R^7)$, (C_1-C_{10})alquil-$N(R^7)$-N=$C(R^8)$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{10}, C_1-C_{10} alquil-OR^{10}, COR^{11}, CO_2R^{11}, SR^{10}, SSR^{10}, SOR^{11}, SO_2R^{11}, C_1-C_{10} alquil-COR^{11}, C_1-C_{10} alquil-SR^{10}, C_1-C_{10} alquil-SOR^{11}, C_1-C_{10} alquil-SO_2R^{11}, halo, $Si(R^{11})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{13} y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{23}, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alquil-OR^{21}, CO_2R^{21}, COR^{21}, $C(S)OR^{21}$, $C(O)SR^{21}$, $C(O)R^{23}$, $C(S)R^{23}$, $CONHR^{22}$, $C(S)NHR^{22}$, $CON(R^{22})_2$, $C(S)N(R^{22})_2$, SR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_6 alquil-CO_2R^{21}, C_1-C_6 alquil-$C(S)OR^{21}$, C_1-C_6 alquil-$C(O)SR^{21}$, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$C(S)R^{23}$, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-$C(S)NHR^{22}$, C_1-C_6 alquil-$CON(R^{22})_2$, C_1-C_6 alquil-$C(S)N(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{15} y R^{16} se seleccionan independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$,

C_1-C_4 alquil-OR^{21}, CSR^{11}, CO_2R^{22}, COR^{23}, $CONHR^{22}$, $CON(R^{22})_2$, SOR^{23}, SO_2R^{23}, C_1-C_6 alquil-CO_2R^{22}, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-$CON(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{19}, C_1-C_6 alquil-R^{19}, C_2-C_6 alquinilo, amino, NHR^{19}, $NR^{19}R^{20}$, C_1-C_6 alquil-NHR^{19}, C_1-C_6 alquil-$NR^{19}R^{20}$, O-R^{21}, C_1-C_4 alquil-OR^{21}, SR^{21}, C_1-C_6 alquil-CO_2R^{21}, C_1-C_6 alquil-$C(S)OR^{21}$, C_1-C_6 alquil-$C(O)SR^{21}$, C_1-C_6 alquil-COR^{23}, C_1-C_6 alquil-$C(S)R^{23}$, C_1-C_6 alquil-$CONHR^{22}$, C_1-C_6 alquil-$C(S)NHR^{22}$, C_1-C_6 alquil-$CON(R^{22})_2$, C_1-C_6 alquil-$C(S)N(R^{22})_2$, C_1-C_6 alquil-SR^{21}, C_1-C_6 alquil-SOR^{23}, C_1-C_6 alquil-SO_2R^{23}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{23}, C_2-C_{10} alquenil-R^{23}, C_2-C_{10} alquinil-R^{23}, C_1-C_{10} alquil-$(R^{23})_2$, C_2-C_{10} alquenil $(R^{23})_2$, CSR^{23}, amino, NHR^{19}, $NR^{20}R^{20}$, $N(R^{19})$-$N(R^{20})(R^{20})$, $C(R^{23})$=N-$N(R^{20})(R^{20})$, N=$N(R^{19})$, $N(R^{19})$-N=$C(R^{20})$, $C(R^{23})$=N-$O(R^{21})$, ON=$C(R^{23})$, C_1-C_{10} alquil-NHR^{19}, C_1-C_{10} alquil-$NR^{20}R^{20}$, (C_1-C_{10})alquil-$N(R^{19})$-$N(R^{20})(R^{20})$, (C_1-C_{10})alquil$C(R^{23})$=N-$N(R^{20})(R^{20})$, (C_1-C_{10})alquil-N=$N(R^{19})$, (C_1-C_{10})alquil-$N(R^{19})$-N=$C(R^{20})$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{21}, C_1-C_{10} alquil-OR^{21},

COR^{23}, CO_2R^{23}, SR^{21}, SSR^{21}, SOR^{23}, SO_2R^{23}, C_1-C_{10} alquil-COR^{23}, C_1-C_{10} alquil-SR^{21}, C_1-C_{10} alquil-SOR^{23}, C_1-C_{10} alquil-SO_2R^{23}, halo, $Si(R^{23})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{29}, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alquil-OR^{27}, CO_2R^{27}, $C(S)OR^{27}$, $C(O)SR^{27}$, $C(O)R^{29}$, $C(S)R^{29}$, $CONHR^{28}$, $C(S)NHR^{28}$, $CON(R^{28})_2$, $C(S)N(R^{28})_2$, SR^{27} SOR^{29}, SO_2R^{29}, C_1-C_6 alquil-CO_2R^{27}, C_1-C_6 alquil-$C(S)OR^{27}$, C_1-C_6 alquil-$C(O)SR^{27}$, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$C(S)R^{29}$, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$C(S)NHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-$C(S)N(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan independientemente de -H, C_1-C_{10} alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, C_1-C_4 alquil-OR^{27}, CSR^{11}, CO_2R^{28}, COR^{29}, $CONHR^{28}$, $CON(R^{28})_2$, SOR^{29}, SO_2R^{29}, C_1-C_6 alquil-CO_2R^{28}, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclil , alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico

cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{23} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-R^{25}, C_1-C_6 alquil-R^{25}, C_2-C_6 alquinilo, amino, NHR^{25}, $NR^{25}R^{26}$, C_1-C_6 alquil-NHR^{25}, C_1-C_6 alquil-$NR^{25}R^{26}$, O-R^{27}, C_1-C_4 alquil-OR^{27}, SR^{27}, C_1-C_6 alquil-CO_2R^{27}, C_1-C_6 alquil-$C(S)OR^{27}$, C_1-C_6 alquil-$C(O)SR^{27}$, C_1-C_6 alquil-COR^{29}, C_1-C_6 alquil-$C(S)R^{29}$, C_1-C_6 alquil-$CONHR^{28}$, C_1-C_6 alquil-$C(S)NHR^{28}$, C_1-C_6 alquil-$CON(R^{28})_2$, C_1-C_6 alquil-$C(S)N(R^{28})_2$, C_1-C_6 alquil-SR^{27}, C_1-C_6 alquil-SOR^{29}, C_1-C_6 alquil-SO_2R^{29}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{24} se selecciona de -H, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{29}, C_2-C_{10} alquenil-R^{29}, C_2-C_{10} alquinil-R^{29}, C_1-C_{10} alquil-$(R^{29})_2$, C_2-C_{10} alquenil-$(R^{29})_2$, CSR^{29}, amino, NHR^{25}, $NR^{26}R^{26}$, $N(R^{25})$-$N(R^{26})(R^{26})$, $C(R^{29})$=N-$N(R^{26})(R^{26})$, N=$N(R^{25})$, $N(R^{25})$-N=$C(R^{26})$, $C(R^{29})$=N-$O(R^{27})$, ON=$C(R^{29})$, C_1-C_{10} alquil-NHR^{25}, C_1-C_{10} alquil-$NR^{26}R^{26}$, (C_1-C_{10})alquil-$N(R^{25})$-$N(R^{26})(R^{26})$,(C_1-C_{10})alquil$C(R^{29})$=N-$N(R^{26})(R^{26})$, (C_1-C_{10})alquil-N=$N(R^{25})$, (C_1-C_{10})alquil-$N(R^{25})$-N=$C(R^{26})$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{27}, C_1-C_{10} alquil-OR^{27}, CO_2R^{29}, COR^{29}, SR^{27}, SSR^{27}, SOR^{29}, SO_2R^{29}, C_1-C_{10} alquil-COR^{29}, C_1-C_{10} alquil-SR^{27}, C_1-C_{10} alquil-SOR^{29}, C_1-C_{10} alquil-SO_2R^{29}, halo, $Si(R^{29})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo,

arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{25} y R^{26} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_4 alquil-R^{35}, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alquil-OR^{33}, CO_2R^{33}, $C(S)OR^{33}$, $C(O)SR^{33}$, $C(O)R^{35}$, $C(S)R^{35}$, $CONHR^{34}$, $C(S)NHR^{34}$, $CON(R^{34})_2$, $C(S)N(R^{34})_2$; SR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_6 alquil-CO_2R^{33}, C_1-C_6 alquil-$C(S)OR^{33}$, C_1-C_6 alquil-$C(O)SR^{33}$, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$C(S)R^{35}$, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$C(S)NHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-$C(S)N(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{27} y R^{28} se seleccionan independientemente de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, C_1-C_4 alquil-OR^{33}, CSR^{11}, CO_2R^{34}, COR^{35}, $CONHR^{34}$, $CON(R^{34})_2$, SOR^{35}, SO_2R^{35}, C_1-C_6 alquil-CO_2R^{34}, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{29} se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquenil-

R^{31}, C_1-C_6 alquil-R^{31}, C_2-C_6 alquinilo, amino, NHR^{31}, $NR^{31}R^{32}$, C_1-C_6 alquil-NHR^{31}, C_1-C_6 alquil-$NR^{31}R^{32}$, O-R^{33}, C_1-C_4 alquil-OR^{33}, SR^{33}, C_1-C_6 alquil-CO_2R^{33}, C_1-C_6 alquil-$C(S)OR^{33}$, C_1-C_6 alquil-$CO(O)SR^{33}$, C_1-C_6 alquil-COR^{35}, C_1-C_6 alquil-$C(S)R^{35}$, C_1-C_6 alquil-$CONHR^{34}$, C_1-C_6 alquil-$C(S)NHR^{34}$, C_1-C_6 alquil-$CON(R^{34})_2$, C_1-C_6 alquil-$C(S)N(R^{34})_2$, C_1-C_6 alquil-SR^{33}, C_1-C_6 alquil-SOR^{35}, C_1-C_6 alquil-SO_2R^{35}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{30} se selecciona de -H, OH, C_1-C_{10} alquilo, C_2-C_{10} alquenilo, C_2-C_{10} alquinilo, C_1-C_{10} alquil-R^{35}, C_2-C_{10} alquenil-R^{35}, C_2-C_{10} alquinil-R^{35}, C_1-C_{10} alquil-$(R^{35})_2$, C_2-C_{10} alquenil-$(R^{35})_2$, CSR^{35}, $N{=}NR^{31}$, amino, NHR^{31}, $NR^{32}R^{32}$, $N(R^{31})$-$N(R^{32})(R^{32})$, $C(R^{35}){=}N$-$N(R^{32})(R^{32})$, $N{=}N(R^{31})$, $N(R^{31})$-$N{=}C(R^{32})$, $C(R^{35}){=}N$-$O(R^{33})$, $ON{=}C(R^{35})$, C_1-C_{10} alquil-NHR^{31}, C_1-C_{10} alquil-$NR^{32}R^{32}$, (C_1-C_{10})alquil-$N(R^{31})$-$N(R^{32})(R^{32})$, (C_1-C_{10})alquil$C(R^{35}){=}N$-$N(R^{32})(R^{32})$, (C_1-C_{10})alquil-$N{=}N(R^{31})$, (C_1-C_{10})alquil-$N(R^{31})$-$N{=}C(R^{32})$, SCN, NCS, C_1-C_{10} alquil SCN, C_1-C_{10} alquil NCS, nitro, ciano, O-R^{33}, C_1-C_{10} alquil-OR^{33}, COR^{35}, SR^{33}, SSR^{33}, SOR^{35}, SO_2R^{35}, C_1-C_{10} alquil-COR^{35}, C_1-C_{10} alquil-SR^{33}, C_1-C_{10} alquil-SOR^{35}, C_1-C_{10} alquil-SO_2R^{35}, halo, $Si(R^{35})_3$, halo C_1-C_{10} alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{31}, R^{32}, R^{33} y R^{34} se seleccionan cada uno independientemente de -H, alquilo, alquenilo, alquinilo, aminoalquilo, hidroxialquilo, alquilamino

alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{35} se selecciona de -H, alquilo, alquenilo, alquinilo, aminoalquilo, OH, alcoxi, amino, alquilamino, dialquilamino, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H, alquilo, alquenilo, alquinilo, aminoalquilo, OH, alcoxi, amino, nitro, ciano, halo, alquilamino, dialquilamino, hidroxialquilo, alquilamino alquilo, dialquilaminoalquilo, alcoxialquilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heterociclilalquilo, y heteroarilalquilo;

R^2, R^3, R^4, R^5, R^{37} y R^{38} cada uno independientemente están ausentes, o se seleccionan de un grupo R^1;

n es 0; y

R^3 y R^4 se juntan de manera opcional para formar un anillo de 5, 6, 7, u 8 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

2. El compuesto de acuerdo con la reivindicación1, en donde cuando Z^2 y Z^3 son ambos nitrógeno, R4 es distinto de pirrol, o de manera opcional cuando Z^4 y Z^5 son ambos nitrógeno y R^a es anillo Q, Q^2 es distinto de nitrógeno.

3. El compuesto de acuerdo con la reivindicación1, en donde R^a se selecciona de un anillo M y un anillo Q.

4. El compuesto de acuerdo con la reivindicación1, en donde R^a es un anillo M.

5. El compuesto de acuerdo con la reivindicación4, en donde el anillo M es un anillo piridina o pirimidina aromática, en donde M^1,M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M5 es carbono, M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono se sustituye con $(L)_nR^1$.

6. El compuesto de acuerdo con la reivindicación1, en donde R^a es un anillo M, en donde el anillo M es un anillo piridina o pirimidina aromática, en donde M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$, M^5 es carbono, M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono se sustituye con $(L)_nR^1$.

7. El compuesto de acuerdo con la reivindicación1, en donde:

R^a es un anillo M que es un es un anillo piridina o pirimidina aromática;

M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono se sustituye con $(L)_nR^1$; y

R^3 y R^4 se juntan de manera opcional para formar un anillo de 5,6,7, u 8 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, O, S, C=O, C=S, S=O, SO_2, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

8. El compuesto de acuerdo con la reivindicación1, en donde:

R^a es un anillo M que es una piridina o pirimidina aromática;

M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono se sustituye con $(L)_nR^1$; y

R^3 y R^4 se juntan de manera opcional para formar un anillo de 6 ó 7 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, C=O, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

9. El compuesto de acuerdo con la reivindicación1, en donde:

R^a es un anillo M que es una piridina o pirimidina aromática;

M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono se sustituye con $(L)_nR^1$; y R^3 y R^4 se juntan de manera opcional para formar un anillo de 6 átomos, donde los átomos en el anillo se seleccionan independientemente de Z^3, Z^4, C=O, C que es mono o di-sustituido con un grupo R^1, y N que es no sustituido o sustituido con un grupo R^1.

10. El compuesto de acuerdo con la reivindicación1, en donde:

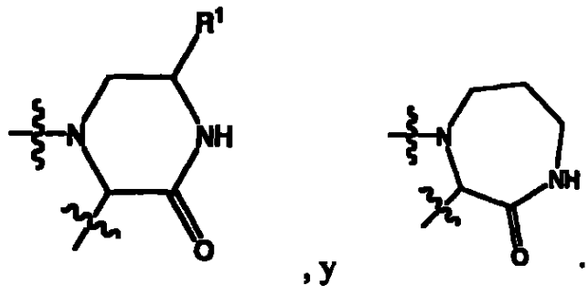
R^a es un anillo M que es un anillo de piridina o pirimidina aromática;

M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 y M^6 se seleccionan independientemente de carbono y nitrógeno y si carbono, el carbono se sustituye con $(L)_nR^1$; y

R^3 y R^4 se unen opcionalmente para formar un anillo que se selecciona de:



, y .

11. El compuesto de acuerdo con la reivindicación1, en donde:

R^a es un anillo M que es una piridina aromática;

M^1, M^3, M^4 y M^6 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

y

M^2 es nitrógeno.

12. El compuesto de acuerdo con la reivindicación1, en donde:

R^a es un anillo M que es una pirimidina aromática:

M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono; y

M^2 y M^6 son nitrógeno.

13. El compuesto de acuerdo con la reivindicación1, en donde:

R^a es un anillo M que es una piridina aromática:

M^1, M^3, M^4 y M^6 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 es nitrógeno;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, hidroxilo, C_1-C_6 alcoxi, C_2-C_6 alquenil-R^{11}, C_1-C_6 alcoxi-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alquilo, hidroxi C_1-C_4 alquilo, amino, amino C_1-C_4 alquil-R^7, halo C_1-C_4 alquilo, C_1-C_6 alquil-NHR^7, carbonitrilo, SR^{10}, halo, NHR^7 NR^8R^9, NHR^7-C_1-C_6 alquilo, NR^8R^9-C_1-C_6 alquilo, nitro, ciano, O-R^{10}, C_1-C_4 alquil-OR^{10}, C_1-C_6 alquil-COR^{11}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, o C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{12};

R^7 y R^8 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, arilo, y arilalquilo, en donde arilo y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^9 y R^{10} se seleccionan cada uno independientemente de -H, hidroxilo, C_1-C_6 alquilo, C_1-C_6 alquil-R^{17}, C_1-C_6 alquil-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alquil-CO_2R^{16}, C_1-C_6 alquil-CONH-R^{16}, C_1-C_6 alquil-$CON(R^{16})_2$, hidroxi C_1-C_4 alquilo, halo C_1-C_4 alcoxi, halo C_1-C_4 alquilo, $Si(R^{13})_2R^{17}$ arilo,

heteroarilo, heterociclilo, arilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxilo, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo, y heterociclilalquilo, en donde heterociclilo, heteroarilalquilo, y heterociclilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, hidroxilo, oxo, C_1-C_6 alquilo, hidroxil C_1-C_6 alquil-R^{11}, C_1-C_{10} alcoxi, amino, amino C_1-C_4 alquil-R^7, NHR^7, $N(R^7)_2$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NHR^8R^9, C_1-C_6 alquil-$N(R^8)_2$, C_1-C_6 alquil-R^{11}, C_1-C_6 alquil-$CO_2R^7R^{11}$, C_1-C_6 alcoxi-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_6 alquil-SR^{10}, halo, halo C_1-C_4 alquilo, halo C_1-C_4 alcoxi, hidroxi C_1-C_4 alquilo, hidroxi C_1-C_4 alcoxi, arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, y heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{13}y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, COR^{23}, y arilo;

R^{15} y R^{16} se seleccionan cada uno independientemente de -H, arilo, arilalquilo, en donde arilo, arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alquil-R^{19}, NHR^{19}, arilo, heteroarilalquilo, y heterociclilalquilo, en donde arilo se sustituye opcionalmente con uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, hidroxilo, C_1-C_{10} alquilo, C_1-C_{10} alcoxi, amino, amino C_1-C_6 alquilo, $N(R^{19})_2$, C_1-C_6 alquil-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, y heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera pcional por uno o más

de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, heteroarilo, heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan cada uno independientemente de -H y C_1-C_6 alquilo;

R^{23} se selecciona de -H y C_1-C_6 alquilo;

R^{24} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, CO_2R^{29}, halo, y halo C_1-C_4 alquilo;

R^{29} se selecciona de -H, y C_1-C_6 alquilo;

R^{30} se selecciona de -H, arilo, heteroarilo, heterociclilo, alquilarilo, arilalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H y halo;

R^2, R^3, R^4, R^{37} y R^{38} se seleccionan cada uno independientemente de un grupo R^1;

14. El compuesto de acuerdo con la reivindicación1, en donde:

R^a es un anillo M que es una pirimidina aromática;

M^1, M^3 y M^4 son carbono y se sustituyen con $(L)_nR^1$;

M^5 es carbono;

M^2 y M^6 son nitrógeno;

R^1 se selecciona de -H, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, hidroxilo, C_1-C_6 alcoxi, C_2-C_6 alquenil-R^{11}, C_1-C_6 alcoxi-R^{11}, COR^{17}, CO_2R^7, $CONHR^7$, $N(R^8)_2$, amino C_1-C_4 alquilo, hidroxi C_1-C_4 alquilo, amino, amino C_1-C_4 alquil-R^7, halo C_1-C_4 alquilo, C_1-C_6 alquil-NHR^7, carbonitrilo, SR^{10}, halo, NHR^7, NR^8R^9, NHR^7-C_1-C_6 alquilo, NR^8R^9-C_1-C_6 alquilo, nitro, ciano, O-R^{10}, C_1-C_4 alquil-OR^{10}, C_1-C_6 alquil-COR^{11}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheterociclilo, alquilheteroarilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, o C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo,

heteroarilo, heterociclilo, mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{12};

R^7 y R^8 se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, C_1-C_4 alquil-R^{11}, C_1-C_6 alquil-$N(R^{13})_2$, CO_2R^{16}, COR^{17}, arilo, y arilalquilo, en donde arilo y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^9 y R^{10} se seleccionan cada uno independientemente de -H, hidroxilo, C_1-C_6 alquilo, C_1-C_6 alquil-R^{17}, C_1-C_6 alquil-NH_2R^{13}, CO_2R^{16}, COR^{17}, C_1-C_6 alquil-CO_2R^{16}, C_1-C_6 alquil-$CONH$-R^{16}, C_1-C_6 alquil-$CON(R^{16})_2$, hidroxi C_1-C_4 alquilo, halo C_1-C_4 alcoxi, halo C_1-C_4 alquilo, $Si(R^{13})_2R^{17}$, arilo, heteroarilo, heterociclilo, arilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{11} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxilo, halo, amino, NHR^{13}, $N(R^{13})_2$, COR^{13}, CO_2R^{17}, halo C_1-C_4 alquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo, y heterociclilalquilo, en donde heterociclilo, heteroarilalquilo, y heterociclilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{12} se selecciona de -H, hidroxilo, oxo, C_1-C_6 alquilo, hidroxil C_1-C_6 alquil-R^{11}, C_1-C_{10} alcoxi, amino, amino C_1-C_4 alquil-R^7, NHR^7, $N(R^7)_2$, C_1-C_6 alquil-NHR^7, C_1-C_6 alquil-NHR^8R^9, C_1-C_6 alquil-$N(R^8)_2$, C_1-C_6 alquil-R^{11}, C_1-C_6 alquil-$CO_2R^7R^{11}$, C_1-C_6 alcoxi-R^{11}, nitro, O-R^{10}, C=O, COR^{11}, CO_2R^{11}, SR^{10}, SOR^{11}, SO_2R^{11}, $NHSO_2R^{11}$, C_1-C_6 alquil-SR^{10}, halo, halo C_1-C_4 alquilo, halo C_1-C_4 alcoxi, hidroxi C_1-C_4 alquilo, hidroxi C_1-C_4 alcoxi, arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo, en donde arilo, heteroarilo, heterociclilo, arilalquilo, heteroarilalquilo, y heterociclilalquilo, y C_1-C_{10} mono- y bicíclico cicloalquilo se sustituyen de manera opcional por uno o más de los grupos definidos por R^{18};

R^{13} y R^{14} se seleccionan cada uno independientemente de -H, oxo, C_1-C_6 alquilo, COR^{23}, y arilo;

R^{15} y R^{16} se seleccionan cada uno independientemente de -H, arilo, arilalquilo, en donde arilo, arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{17} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alquil-R^{19}, NHR^{19}, arilo, heteroarilalquilo, y heterociclilalquilo, en donde arilo se sustituye opcionalmente con uno o más de los grupos definidos por R^{24};

R^{18} se selecciona de -H, oxo, hidroxilo, C_1-C_{10} alquilo, C_1-C_{10} alcoxi, amino, amino C_1-C_6 alquilo, $N(R^{19})_2$, C_1-C_6 alquil-$N(R^{19})_2$, CO_2R^{23}, SR^{21}, halo, halo C_1-C_4 alquilo, arilo, heteroarilo, y heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{24};

R^{19} y R^{20} se seleccionan cada uno independientemente de -H, C_1-C_6 alquilo, heteroarilo, heterociclilo, en donde arilo, heteroarilo, y heterociclilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{30};

R^{21} y R^{22} se seleccionan cada uno independientemente de -H y C_1-C_6 alquilo;

R^{23} se selecciona de -H y C_1-C_6 alquilo;

R^{24} se selecciona de -H, C_1-C_6 alquilo, C_1-C_6 alcoxi, CO_2R^{29}, halo, y halo C_1-C_4 alquilo;

R^{29} se selecciona de -H, y C_1-C_6 alquilo;

R^{30} se selecciona de -H, arilo, heteroarilo, heterociclilo, alquilarilo, arilalquilo, en donde arilo, heteroarilo, heterociclilo, alquilarilo, y arilalquilo, se sustituyen de manera opcional por uno o más de los grupos definidos por R^{36};

R^{36} se selecciona de -H y halo;

R^2, R^3, R^4, R^{37} y R^{38} se seleccionan cada uno independientemente de un grupo R^1;

15. Un compuesto inhibidor de MK-2 que se enumera en Tabla I o Tabla II.

16. El compuesto de acuerdo con la reivindicación15, en donde el compuesto se selecciona del grupo conformado por:

trifluoroacetato de ácido 1-(2-aminoetil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxílico,
diclorhidrato de ácido 1-(3-aminopropil)-3-[2-(3-nitrofenil)piridin-4-il]-1H-pirazol-5-carboxílico,
6-(aminometil)-2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona,
trifluoroacetato de ácido 1-(2-aminoetil)-3-[2-[(E)-2-feniletenil]piridin-4-il}-1H-pirazol-5-carboxílico,
diclorhidrato de ácido 1-(2-aminoetil)-3-{2-[4-(hidroximetil)fenil]piridin-4-il}-1H-pirazol-5-carboxílico,
6-(hidroximetil)-2-(2-quinolin-3-ilpiridin-4-il)-6,7-dihidropirazolo[1,5-a]pirazin-4(5H)-ona, y
diclorhidrato de ácido 1-(3-aminopropil)-3-(2-quinolin-3-ilpiridin-4-il)-1H-pirazol-5-carboxílico, y sus mezclas.

17. Un método de inhibir MK-2, método que comprende poner en contacto MK-2 con por lo menos un compuesto que tiene la estructura descrita en la reivindicación 1.

18. Un método de inhibir MK-2, método que comprende poner en contacto MK-2 con por lo menos un compuesto que se selecciona de los compuestos descritos en la reivindicación 15.

19. Un método de prevenir o tratar una enfermedad o trastorno mediada por TNFα en un individuo, método que comprende administrar al individuo una cantidad efectiva de un compuesto inhibidor de MK-2 que tiene la estructura descrita en la reivindicación 1.

20. El método de acuerdo con la reivindicación19, en donde el individuo es uno necesitado de tal prevención o tratamiento.

21. El método de acuerdo con la reivindicación19, en donde el individuo es un mamífero.

22. El método de acuerdo con la reivindicación 19, en donde el individuo es un humano.

23. El método de acuerdo con la reivindicación19, en donde la enfermedad o trastorno mediada por TNFα es uno que se selecciona del

grupo conformado por trastornos de las articulaciones y el tejido conectivo, trastornos de neoplasia, trastornos cardiovasculares, trastornos óticos, trastornos oftámicos, trastornos respiratorios, trastornos gastrointestinales, trastornos relacionados con angiogénesis, trastornos inmunitarios, trastornos alérgicos, trastornos de la nutrición, enfermedades y trastornos infecciosos, trastornos endocrinos, trastornos metabólicos, trastornos neurales y neurodegenerativos, trastornos psiquiátricos, trastornos hepáticos y biliares, trastornos del esqueleto mucular, trastornos genitourinarios, trastornos ginecológicos y obstétricos, trastornos ocasionados por lesiones y traumas, trastornos quirúrgicos, trastornos dentales y orales, trastornos de disfunción sexual, trastornos cutáneos, trastornos sanguíneos, y trastornos por envenenamiento.

24. El método de acuerdo con la reivindicación 19, en donde la enfermedad o trastorno mediado por TNFα se selecciona del grupo conformado por: artritis, artritis reumatoide, espondiloartopatías, artritis gotosa, osteoartritis, lupus sistémico ertematoso, artritis de la juventud, asma, bronquitis, cólicos menstruales, tendinitis, bursitis, lesiones o trastornos del tejido conectivo, enfermedades relacionadas con la piel, psoriasis, eczema, quemaduras, dermatitis, afecciones gastrointestinales, enfermedad del intestino inflamado, úlcera gástrica, várices gástricas, enfermedad de Crohn, gastritis, síndrome del intestino irritable, colitis ulcerosa, cáncer, cáncer colorrectal, infecciones por herpes simplex, VIH, edema pulmonar, cálculos renales, lesiones menores, cicatrización, vaginitis, candidiasis, espondiloartrosis lumbar, vasculopatías, jaquecas, cefaleas de los senos, cefaleas por tensión, dolor de dientes, periarteritis nodosa, tiroiditis, anemia aplásica, enfermedad de Hodgkin, esclerodoma, fiebre reumática, diabetes tipo I, myasthenia gravis, esclerosis múltiple, sarcoidosis, síndrome nefrótico, síndrome de Behcet, polimiositis, gingivitis, hipersensibilidad, hinchazón a raíz de una lesión, isquemia del miocardio, enfermedades oftálmicas, retinitis, retinopatías, conjuntivitis, uveítis, fotofobia ocular, lesión aguda al tejido ocular, inflamación pulmonar, infecciones virales, fibrosis quística, trastornos del sistema

nervioso central, demencias corticales, y enfermedad de Alzheimer.

25. Un método de prevenir o tratar una enfermedad o trastorno mediado por TNFα en un individuo, método que comprende administrar al individuo por lo menos un compuesto inhibidor de MK-2 que se selecciona del grupo conformado por los compuestos descritos en la reivindicación 15.

26. Una composición terapéutica que comprende un compuesto que tiene la estructura descrita en la reivindicación 1.

27. Una composición terapéutica que comprende por lo menos un compuesto inhibidor de MK-2 que se describe en la reivindicación 15.

28. Una composición farmacéutica que comprende un vehículo farmacéuticamente aceptable y por lo menos un compuesto inhibidor de MK-2 que tiene la estructura descrita en la reivindicación 1.

29. La composición farmacéutica de acuerdo con la reivindicación 28, en donde el compuesto inhibidor de MK-2 tiene una IC_{50} para MK-2 de no más de 0.1 mM.

30. Un estuche que comprende una formulación farmacéutica que incluye una cantidad terapéuticamente efectiva de por lo menos un compuesto inhibidor de MK-2 que tiene una estructura descrita en la reivindicación 1.

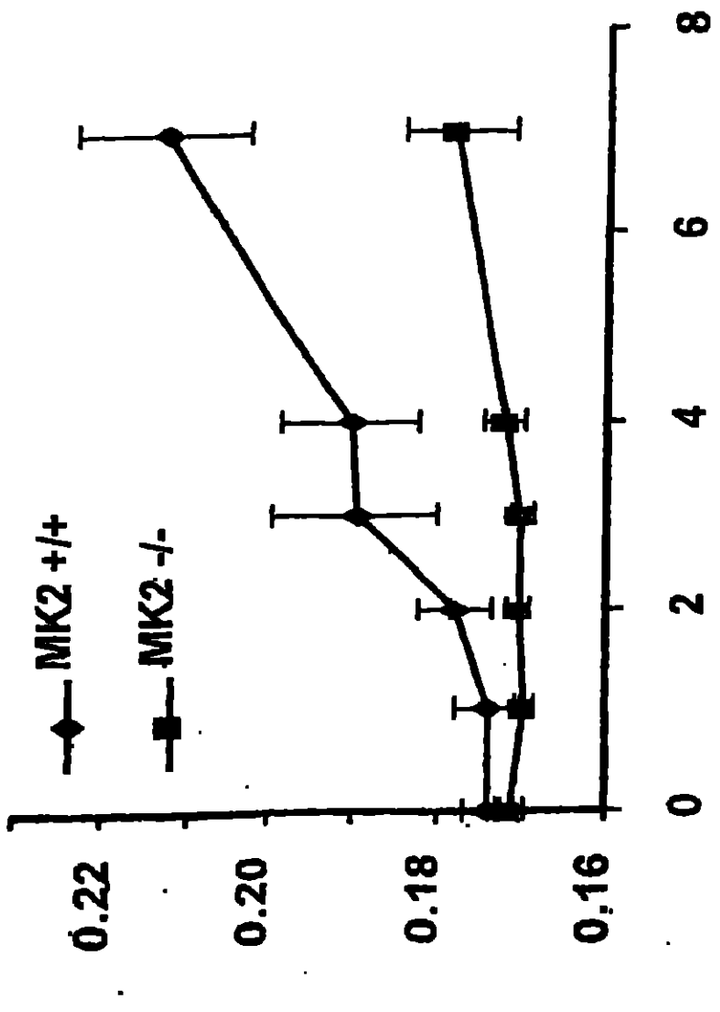


FIGURA 1

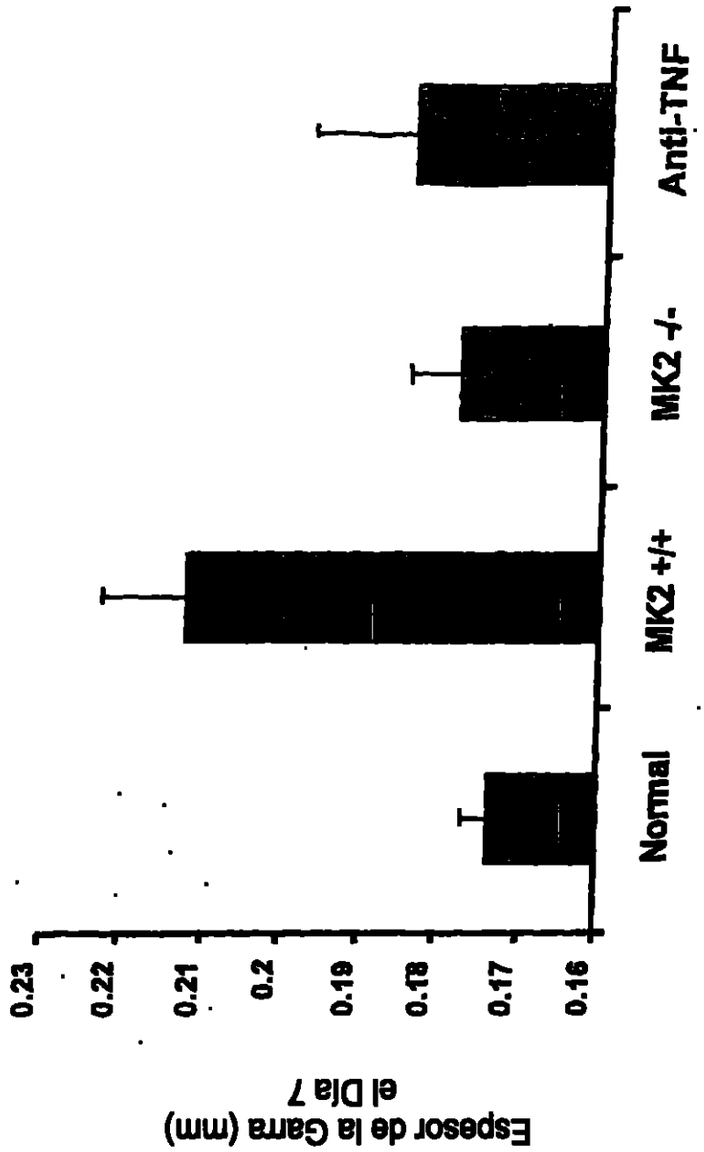

Espesor de la Garra (mm)
el Dia 7
0.23
0.22
0.21
0.2
0.19
0.18
0.17
0.16
Normal
MK2 +/+
MK2 -/-
Anti-TNF

FIGURA 2

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18438/09099

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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-EASY Version 2.92 (updated 01.11.2003)
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	18438/09099
I	Title of invention	ACYCLIC PYRAZOLE COMPOUNDS FOR THE INHIBITION OF MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	PHARMACIA CORPORATION
II-5	Address:	Mail Zone MC5S 575 Maryville Centre Drive St. Louis, MO 63141 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	(908) 901-8000
II-9	Facsimile No.	(908) 901-8379
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)	HANAU, Cathleen, E.
III-1-5	Address:	15551 Wendimill Drive Chesterfield, MO 63017 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

PCT REQUEST

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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)	MERSHON, Serena, Marie
III-2-5	Address:	303 Spring Street Bessemer, MI 49911 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)	GRANETO, Matthew, J.
III-3-5	Address:	352 Hartwell Ct. Chesterfield, MO 63017 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)	MEYERS, Marvin, J.
III-4-5	Address:	4006 Summerfield Parkway Saint Charles, MO 63304 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)	HEGDE, Shridhar, G.
III-5-5	Address:	130 Holly Garden Drive Ballwin, MO 63021 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)	BUCHLER, Ingrid, P.
III-6-5	Address:	7627 Delmar Blvd., Apt. 2 South University City, MO 63130 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US

PCT REQUEST

Original (for SUBMISSION) - printed on 19.12.2003 11:58:10 AM

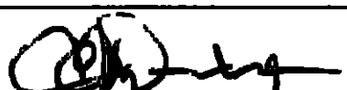
III-7	Applicant and/or inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	WU, Kun, K.
III-7-5	Address:	1101-I Olive Lake Drive St. Louis, MO 63132 United States of America
III-7-6	State of nationality	CA
III-7-7	State of residence	US
III-8	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)	LIU, Shuang
III-8-5	Address:	302 Polsinelli Dr. Schenectady, NY 12303 United States of America
III-8-6	State of nationality	CN
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)	MACRO, Kassoom
III-9-5	Address:	106 Teneyck Place, Apt. 10 Guilderland, NY 12084 United States of America
III-9-6	State of nationality	BF
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	NELSON MULLINS RILEY & SCARBOROUGH, LLP
IV-1-2	Address:	P.O. Box 11070 Columbia, SC 29211-1070 United States of America
IV-1-3	Telephone No.	(864) 250-2238
IV-1-4	Facsimile No.	(803) 256-7500
IV-1-5	e-mail	ced@nmrs.com
IV-1-5	Agent's registration No.	35,124

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI 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 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	20 December 2002 (20.12.2002)
VI-1-2	Number	60/434,962
VI-1-3	Country	US

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18438/09099

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VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	240	-
IX-3	Claims	21	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	2	-
IX-7	TOTAL	270	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Transmittal Letter to USRO	-
IX-18	Other (specified):	Return Postcard	-
IX-18	Other (specified):	Unexecuted PCT Power of Attorney	-
IX-19	Figure of the drawings which should accompany the abstract	1	
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	NELSON MULLINS RILEY & SCARBOROUGH, LLP	
X-1-2	Name of signatory	Charles E. Dunlap	
X-1-3	Capacity	Agent of Record	

PCT REQUEST

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/US
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	

PCT (ANNEX - FEE CALCULATION SHEET)

18438/09099

Original (for SUBMISSION) - printed on 19.12.2003 11:58:10 AM

(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-EASY Version 2.92 (updated 01.11.2003)		
0-9	Applicant's or agent's file reference		18438/09099		
2	Applicant		PHARMACIA CORPORATION, et al.		
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee	T	⇨	240	
12-2-1	Search fee	S	⇨	700	
12-2-2	International search to be carried out by		US		
12-3	International fee				
	Basic fee				
	(first 30 sheets)	b1	476		
12-4	Remaining sheets		240		
12-5	Additional amount	(X)	12		
12-6	Total additional amount	b2	2,880		
12-7	b1 + b2 =	B	3,356		
12-8	Designation fees				
	Number of designations contained in international application		99		
12-9	Number of designation fees payable (maximum 5)		5		
12-10	Amount of designation fee	(X)	104		
12-11	Total designation fees	D	520		
12-12	PCT-EASY fee reduction	R	-148		
12-13	Total international fee (B+D-R)	I	⇨	3,728	
12-14	Fee for priority document				
	Number of priority documents requested		1		
12-15	Fee per document	(X)	20		
12-16	Total priority document fee	P	⇨	20	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	4,688	
12-19	Mode of payment		cheque		
12-20	Deposit account instructions				
	The receiving Office:		United States Patent and Trademark Office (USPTO) (RO/US)		
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.		✓		

The demand must be filed directly wi... competent International Preliminary Examining Authority ... two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

348
399

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 18438/09099
International application No. PCT/US03/40932	International filing date *(day/month/year)* 19 December 2003	(Earliest) Priority date *(day/month/year)* 20 December 2002
Title of invention ACYCLIC PYRAZOLE COMPOUNDS FOR THE INHIBITION OF MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No. (908) 901-8000
PHARMACIA CORPORATION 700 Chesterfield Parkway West Chesterfield, MO 63017-1732 United States of America	Facsimile No. (908) 901-8379
	Teleprinter No.
	Applicant's registration No. with the Office

State *(that is, country)* of nationality: US	State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HANAU, Cathleen E.
15551 Wendimill Drive
Chesterfield, MO 63017
United States of America

State *(that is, country)* of nationality: US	State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MERSHON, Serena Marie
303 Spring Street
Bessemer, MI 49911
United States of America

State *(that is, country)* of nationality: US	State *(that is, country)* of residence: US

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US03/40932

400
2 of 2

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GRANETO, Matthew J.
352 Hartwell Ct.
Chesterfield, MO 63017
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MEYERS, Marvin J.
4006 Summerfield Parkway
Saint Charles, MO 63304
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HEGDE, Shridhar G.
130 Holly Garden Drive
Ballwin, MO 63021
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BUCHLER, Ingrid P.
7627 Delmar Blvd., Apt. 2
South University City, MO 63130
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

☒ Further applicants are indicated on another continuation sheet.

International application No.
PCT/US03/40932

35 PCT 401

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WU, Kun K.
1101-I Olive Lake Drive
St. Louis, MO 63132
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LIU, Shuang
302 Polelnelli Dr.
Schenectady, NY 12303
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CN	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NACRO, Kassoom
106 Teneyck Place, Apt. 10
Guilderland, NY 12084
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
BF	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/US03/40932

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Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NELSON MULLINS RILEY & SCARBOROUGH, LLP
1320 Main Street
17th Floor
Columbia, SC 29201
United States of America

Telephone No.
(864) 250-2238

Facsimile No.
(803) 256-7500

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☒ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).

4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

International application No.
PCT/US03/40932

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ tables in computer readable form related to a sequence listing
8. ☒ other *(specify)*: Transmittal Letter to USRO and Return Postcard

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Charles E. Dunlap, Reg. No. 35,124
Agent of Record

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

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PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US03/40932	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 18438/09099	Date stamp of the IPEA

Applicant
PHARMACIA CORPORATION

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	$600.00	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	$162.00	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	$762.00 TOTAL		

MODE OF PAYMENT

- ☐ authorization to charge deposit account with the IPEA (see below)
- ☒ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
(This mode of payment may not be available at all IPEAs)

IPEA/ US

☐ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 50-2548

Date: 14 June 2004

Name: Charles F. Dunlap, Reg.# 35,124

Signature:

Form PCT/IPEA/401 (Annex) (January 2004)

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 18438/08099	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/40992	International filing date (*day/month/year*) 19 December 2003 (19.12.2003)	(Earliest) Priority Date (*day/month/year*) 20 December 2002 (20.12.2002)
Applicant PHARMACIA CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☒ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established by this Authority to read as follows:

The title is too many words. The new title is "Acyclic Pyrazole Compounds".

5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant. ☒ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/40932

2996 406

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 2-30
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/40932

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 401/14
US CL : 546/167

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/167

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6469028 B1 (KLEIN et al) 22 October 2002 (22.10.2002), column 4, lines 1-67, and column 5, lines 1-12.	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2004 (29.03.2004)	02 JUL 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Sonya Wright Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of Box I Reason 2:
In these claims, the numerous variables (e.g. Ra, R2, R3, R4, R5, Z1, Z2, Z3, etc. . .) and their voluminous complex meanings and their many permutations and combinations make it difficult to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus, a meaningful search cannot be carried out on the same. A search will be made on the first discernable invention, which is structure Numbers 1 and 7 of Table 1 on page 45.

PATENT COOPERATION TREATY

2pk 409.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

NELSON MULLINS RILEY & SCARBOROUGH, LLP
P.O. Box 11070
Columbia, SC 29211-1070
United States of America

Date of mailing (day/month/year)
11 March 2004 (11.03.2004)

RECEIVED
MAR 2 4 2004
NELSON MULLINS
COLUMBIA OFFICE

Applicant's or agent's file reference
18438/09099

IMPORTANT NOTIFICATION

International application No.
PCT/US2003/040932

International filing date (day/month/year)
19 December 2003 (19.12.2003)

International publication date (day/month/year)
Not yet published

Priority date (day/month/year)
20 December 2002 (20.12.2002)

Applicant
PHARMACIA CORPORATION 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 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
20 Dece 2002 (20.12.2002)	60/434,962	US	08 Marc 2004 (08.03.2004)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338-7080

Authorized officer
Norbert RIGHETTO

Telephone No. (41-22) 338 9889

UNITED STATES PATENT AND TRADEMARK OFFICE

410 10/18438/09060 MO

OCTOBER 29, 2003

Chief Financial Officer and Chief Administrative Officer
Washington, DC 20231
www.uspto.gov

NELSON MULLINS RILEY & SCARBOROUGH
CHARLES E. DUNLAP
KEENAN BUILDING, THIRD FLOOR
1330 LADY STREET
COLUMBIA, SC 29201

PTAS RECEIVED

102454871A

HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

6794-000174/PS1

Transferred

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/19/2003 REEL/FRAME: 014081/0623
NUMBER OF PAGES: 7

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ANDERSON, DAVID R. DOC DATE: 02/20/2003

ASSIGNOR:
PHILLION, DENNIS P. DOC DATE: 03/20/2003

ASSIGNOR:
MEYERS, MARVIN J. DOC DATE: 03/20/2003

ASSIGNOR:
HEGDE, SHRIDHAR G. DOC DATE: 03/20/2003

ASSIGNOR:
REITZ, DAVID B. DOC DATE: 03/20/2003

ASSIGNEE:
PHARMACIA CORPORATION
575 MARYVILLE CENTRE DRIVE
MAIL ZONE MC5S
ST. LOUIS, MISSOURI 63141

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COLUMBIA OFFICE

411

014081/0623 PAGE 2

SERIAL NUMBER: 60434962
PATENT NUMBER:

FILING DATE: 12/20/2002
ISSUE DATE:

MARY BENTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

05-22-03

412

PATENT

Practitioner's Docket No. 18438/09060

102454871

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Mail Stop Assignment Recordation Services
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Attached please find an assignment (document) for recordal. S.19.03

IDENTIFICATION OF APPLICATION(S) AND/OR PATENT(S) FOR ASSIGNMENT (DOCUMENT) RECORDAL (37 C.F.R. § 3.21 and 37 C.F.R. § 3.31(a)(4))

1. This assignment is for the following patent application and/or issued patent:

   a. Provisional application: 60/434,962, filed on December 20, 2002

TOTAL NUMBER OF APPLICATIONS AND/OR PATENTS AND TOTAL FEE

2. A. The total number of applications and/or patents identified in this cover sheet is: 1.

   B. The total fee is (37 C.F.R. Section 1.21(h)):

   1 x $40.00 = $40.00

CERTIFICATION UNDER 37 C.F.R. §§ 1.8(a) and 1.10*

(When using Express Mail, the Express Mail label number is mandatory; Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☑ deposited with the United States Postal Service in an envelope addressed to the Director of the United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

37 C.F.R. § 1.8(a)

☑ with sufficient postage as first class mail.

37 C.F.R. § 1.10*:

☐ as "Express Mail Post Office to Addressee" Mailing Label No. _____ (mandatory)

TRANSMISSION

☐ facsimile transmitted to the Patent and Trademark Office, (703) ____-____

Signature

Date: May 16, 2003

Anna A. Von
(type or print name of person certifying)

* *Only the date of filing (§ 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under § 1.8 continues to be taken into account in determining timeliness. See § 1.703(f). Consider "Express Mail Post Office to Addressee" (§ 1.10) or facsimile transmission (§ 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.*

05/19/2003 KZEMBTE 00000063 60434962
02 FC:8021 40.00 OP

403/413

C. Payment of fee is made by:

Attached is Check No. 22919 in the amount of $90.00, including the $40.00 required fee for assignment recordal.

Charge any additional fees required by this paper or credit any overpayment to Account No. 50-2548.

A duplicate of this paper is attached.

NAME OF PARTIES CONVEYING INTEREST
(37 C.F.R. § 3.31(a)(1))

3. The parties conveying interest are:

David R. Anderson
Dennis P. Phillion
Marvin J. Meyers
Shridhar G. Hegde
David B. Reitz

NAME AND ADDRESS OF PARTY(IES) RECEIVING INTEREST
(37 C.F.R. § (a)(2))

4. The rights are being conveyed to:

Pharmacia Corporation
Mail Zone MC5S
575 Maryville Centre Drive
St. Louis, MO 63141

DESCRIPTION OF INTEREST CONVEYED OR TRANSACTION RECORDED (37 C.F.R. § 3.31(a)(3))

5. The accompanying document intends to accomplish an assignment.

NAME AND ADDRESS OF PARTY TO WHOM CORRESPONDENCE SHOULD BE MAILED (37 C.F.R. § 3.31 (a)(5))

6. Please address correspondence to:

Name: Charles E. Dunlap
Address: Nelson Mullins Riley & Scarborough
Keenan Building, Third Floor
1330 Lady Street
Columbia, SC 29201
Telephone No.: 864-250-2238

DATE ASSIGNMENT (DOCUMENT) EXECUTED
(37 C.F.R. § 3.31(a)(7))

7. The attached assignment (document) was executed by David R. Anderson on February 20, 2003.
The attached assignment (document) was executed by Dennis P. Phillion on March 20, 2003.
The attached assignment (document) was executed by Marvin I. Meyers on March 20, 2003.
The attached assignment (document) was executed by Shridhar G. Hegde on March 20, 2003.
The attached assignment (document) was executed by David B. Reitz on March 20, 2003.

LANGUAGE OF ASSIGNMENT (DOCUMENT) TO BE RECORDED

8. The attached document is in the English language.

ORIGINAL DOCUMENT OR TRUE COPY SUBMITTED

9. Submitted herewith is the original document.

STATEMENT (37 C.F.R. § 3.31(a)(9)) AND SIGNATURE (37 C.F.R. § 3.31(a)(10))

10. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Date: May 16, 2005

Signature of Practitioner

Reg. No.: 35,124
Tel. No.: 864-250-2238

Charles E. Dunlap
Nelson Mullins Riley & Scarborough
Keenan Building, Third Floor
1330 Lady Street
Columbia, SC 29201

TOTAL NUMBER OF PAGES BEING SUBMITTED

11. The total number of pages being submitted, including documents is: 7.

DOCKET NO: 18438/09060 (01508/1)

ASSIGNMENT

WHEREAS, I/WE, the undersigned, have made certain invention or inventions which are disclosed in patent application(s) and/or provisional patent application(s) entitled:

MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2 INHIBITING COMPOUNDS

The specification of which was filed as a Provisional Application on December 20, 2002 and given Serial Number 60/434,962.

WHEREAS, PHARMACIA CORPORATION, having its address at Mail Zone MC5S, 575 Maryville Centre Drive, St. Louis, Missouri, 63141, U.S.A., a business organized under the laws of the State of Delaware, is desirous of acquiring the entire right, title and interest in and to said invention or inventions and any and all patents to be obtained therefor;

NOW, THEREFORE, FOR GOOD AND VALUABLE CONSIDERATION, the receipt of which is hereby acknowledged, I/WE do hereby sell, assign and transfer to said PHARMACIA CORPORATION, its successors and assigns, the entire right, title and interest in and to said invention or inventions, in any form or embodiment thereof, and in and to said application(s); and in and to any and all applications filed in any country based thereon, including the right to file application in countries other than the country of priority filing under the provisions of any international convention; also in and to any and all improvements on said invention or inventions now or hereafter made by me/us as employee(s), agent(s) or contractor(s) of said PHARMACIA CORPORATION, also the entire right, title and interest in and to any and all patents, including reissues and extensions thereof, to be obtained in any country upon said invention, inventions or improvements, and any and all continuing applications, including divisional, continuation and continuation-in-part applications, substitute applications, and applications claiming benefit of an earlier filed provisional application, which may be filed upon said invention, inventions or improvements in any country; and

I/WE hereby authorize and request the issuing authority to issue any and all patents on said application or applications to said PHARMACIA CORPORATION, as assignee of the entire interest.

I/WE further agree, without any payment by PHARMACIA CORPORATION, other than in reimbursement of reasonable expenses I/we may incur, to communicate to said PHARMACIA CORPORATION, its representatives or agents, any facts relating to said invention, inventions or improvements, including evidence for purposes of interference, opposition or other legal proceedings, whenever requested; testify in any interference, opposition or other legal proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective.

476

IN TESTIMONY WHEREOF, I have hereto set my hand on the date set after my signature.

Signature: _____ Date: 2/20/03

Name: David R. Anderson

Residence: 2 Lodge Ct., Lake St. Louis, MO 63367 U.S.A.

State of Missouri)
)
County of St. Louis)

On this 20 day of February, 2003 before me personally appeared David R. Anderson to me known to be the person who executed the foregoing instrument and acknowledged that he executed the same as his free act and deed; in testimony whereof I have hereto set my hand and official seal on the day last above-written.

_____
Notary Public

My Commission expires _____

LINDA HALEY
Notary Public - Notary Seal
State of Missouri
St Louis County
My Commission Expires Oct 23, 2004

IN TESTIMONY WHEREOF, I have hereto set my hand on the date set after my signature.

Signature: _____ Date: 3/20/03

Name: Dennis P. Phillion

Residence: 1626 Watson, St. Charles, MO 63301 U.S.A.

State of Missouri)
)
County of St. Louis)

On this 20 day of March, 2003 before me personally appeared Dennis P. Phillion, to me known to be the person who executed the foregoing instrument and acknowledged that he executed the same as his free act and deed; in testimony whereof I have hereto set my hand and official seal on the day last above-written.

_____
Notary Public

My Commission expires 8-16-06

JOYCE H. KREBS
NOTARY PUBLIC - STATE OF MISSOURI
MY COMMISSION EXPIRES 08/16/2006
ST. LOUIS COUNTY

417

IN TESTIMONY WHEREOF, I have hereto set my hand on the date set after my signature.

Signature: _____ Date: 3/20/03

Name: Marvin J. Meyers

Residence: 4006 Summerfield Parkway, St. Charles, MO 63304 U.S.A.

State of Missouri)
County of St. Louis)

On this 20 day of March, 2003, before me personally appeared Marvin J. Meyers, to me known to be the person who executed the foregoing instrument and acknowledged that he executed the same as his free act and deed; in testimony whereof I have hereto set my hand and official seal on the day last above-written.

_____ Notary Public

My Commission expires 8-10-06

JOYCE H. KREBS
NOTARY PUBLIC - STATE OF MISSOURI
MY COMMISSION EXPIRES 08/10/2006
ST. LOUIS COUNTY

IN TESTIMONY WHEREOF, I have hereto set my hand on the date set after my signature.

Signature: Shridhar Hegde Date: 3/20/03

Name: Shridhar G. Hegde

Residence: 130 Holly Garden Drive, Ballwin, MO 63021 U.S.A.

State of Missouri)
County of St. Louis)

On this 20 day of March, 2003 before me personally appeared Shridhar G. Hegde, to me known to be the person who executed the foregoing instrument and acknowledged that he executed the same as his free act and deed; in testimony whereof I have hereto set my hand and official seal on the day last above-written.

_____ Notary Public

My Commission expires 8-10-06

JOYCE H. KREBS
NOTARY PUBLIC - STATE OF MISSOURI
MY COMMISSION EXPIRES 08/10/2006
ST. LOUIS COUNTY

418

IN TESTIMONY WHEREOF, I have hereto set my hand on the date set after my signature.

Signature: David B. Reitz Date: 3/20/03

Name: David B. Reitz

Residence: 14814 Pleasant Ridge Court, Chesterfield, MO 63017 U.S.A.

State of Missouri)
County of St. Louis)

On this 20 day of March, 2003 before me personally appeared David B. Reitz, to me known to be the person who executed the foregoing instrument and acknowledged that he executed the same as his free act and deed; in testimony whereof I have hereto set my hand and official seal on the day last above-written.

Joyce H. Krebs
Notary Public

JOYCE H. KREBS
NOTARY PUBLIC - STATE OF MISSOURI
MY COMMISSION EXPIRES 08/10/2006
ST. LOUIS COUNTY

My Commission expires 8-10-06

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

6794-000194/PS1
Transferred

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/434,982	12/20/2002		210	18438/09060 (01506/1)	4		

CONFIRMATION NO. 9794

Charles E. Dunlap
Nelson Mullins Riley & Scarborough
Keenan Building, Third Floor
1330 Lady Street
Columbia, SC 29201

RECEIVED

UPDATED FILING RECEIPT

"OC000000010282290"

HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

Date Mailed: 06/17/2003

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

David R. Anderson, Lake St. Louis, MO;
Dennis P. Phillion, St. Charles, MO;
Marvin J. Meyers, Saint Charles, MO;
Shridhar G. Hegde, Ballwin, MO;
David B. Reitz, Chesterfield, MO;

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JUN 20 2003
NELSON MULLINS
COLUMBIA OFFICE

If Required, Foreign Filing License Granted: 03/17/2003

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

DOCKETED BY
20 DEC 03 FFD
PSC

Title

Mitogen activated protein kinase-activated protein kinase-2 inhibiting compounds

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

4304c

XX421

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *District of Columbia*
   United States of America

2. This public document has been signed by MELISSA O. JACKSON

3. acting in the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBI

4. bears the seal/stamp of MELISSA O. JACKSON, NOTARY PUBLIC IN AND FOR THI

DISTRICT OF COLUMBIA

CERTIFIED

5. at Washington, D. C.

6. the 6 day of FEBRUARY 2004

7. by *Secretary of the District of Columbia*

8. No. 121542

9. Seal/Stamp

10. Signature

SHERRYL H. NEWMAN

CONSULADO CUARENTA Y SEIS
CIRCUITO DE BOGOTA, HAGO CONSTAR
QUE ESTA COPIA FOTOSTATICA CONCUERDA
CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
16 JUN 2005
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SEIS

Pharmacia Ref: SO3435/1/Columbia
HDP Ref: 6794S-100009/CO

A22

Brigard & Castro
BOGOTA - COLOMBIA

POWER OF ATTORNEY

I (We) PHARMACIA CORPORATION

domiciled in
700 CHESTERFIELD PARKWAY WEST
CHESTERFIELD, MISSOURI 63017-1732
UNITED STATES OF AMERICA

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, 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 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; penal demands, actions of indemnities for 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

PODER

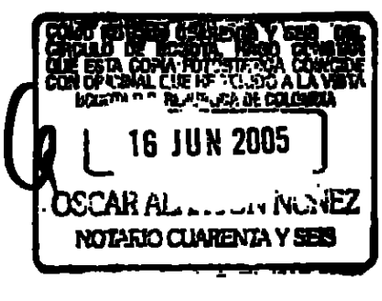
Yo (nosotros) PHARMACIA CORPORATION

domiciliado(s) en
700 CHESTERFIELD PARKWAY WEST
CHESTERFIELD, MISSOURI 63017-1732
ESTADOS UNIDOS DE AMÉRICA

Nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, 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 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 creyeren

Legalization by Apostille is Required



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 appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, 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.

This Power of Attorney is specially granted for Colombian Patent Application entitled:

STABILIZED ORAL SUSPENSION FORMULATION

Granted and signed in

NEW YORK, NEW YORK
UNITED STATES OF AMERICA

This 13th day January of 2004

Signature _____

PHARMACIA CORPORATION
BY J. TREVOR LUMB
ASSISTANT SECRETARY

conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

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: **RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA**, 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.

Este poder se concede especialmente para la solicitud de Patente Colombiana titulada:

Otorgado y firmado en

hoy de de 200_

Firma
Nombre
Cargo

Legalization by Apostille is Required

COMO NOTARIO CUARENTA Y SEIS DEL CIRCULO DE BOGOTA, D.C. CERTIFICO QUE ESTA COPIA FOTOSTATICA CONCUERDA CON ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
16 JUN 2005
OSCAR ALFONSO GOMEZ
NOTARIO CUARENTA Y SEIS

NOTARIAL CERTIFICATE (CORPORATION)

On this 13th day of January of 2004 personally appeared before me

J. TREVOR LUMB

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

of **PHARMACIA CORPORATION**

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
and that he (she) who grants the present power of attorney is its Representative.

Notary Public Rosalba Olivieri

Commission Expires December 30, 2006

ROSALBA OLIVIERI
Notary Public, State of New York
No. 01OL6088628
Qualified in Queens County
Certificate Filed in New York County
Commission Expires December 30, 2006

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 es

de **PHARMACIA CORPORATION**

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 cuál se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

y que quien confiere el presente poder es su representante.

Notario Público (sello)

Legalization by Apostille is Required

COMO NOTARIO CUARENTA Y SEIS DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
16 JUN 2005
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SEIS

225

NOTARIAL CERTIFICATE (CORPORATION)

On this 13th day of January of 2004 personally appeared before me

J. TREVOR LUMB

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

of **PHARMACIA CORPORATION**

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
and that he (she) who grants the present power of attorney is its Representative.

Notary Public Rosalba Oliveri

My Commission Expires December 30, 2006

ROSALBA OLIVERI
Notary Public, State of New York
No. 01OL6086628
Qualified in Queens County
Certificate Filed in New York County
Commission Expires December 30, 2006

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 es

de **PHARMACIA CORPORATION**

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 de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

y que quien confiere el presente poder es su representante.

Notario Público (sello)

CUARENTA Y SEIS DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FIEL ESTA DE ACUERDO CON ORIGINAL QUE SE ME PRESENTO A LA VISTA
BOGOTA D.C. REP. DE COLOMBIA
16 JUN 2005
OSCAR ALBERTO NUÑEZ
NOTARIO CUARENTA Y SEIS

Legalization by Apostille is Required

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TRADUCCION AL ESPAÑOL del documento de poder de PHARMACIA C RP RATION, domiciliada en 700 CHESTERFIELD PARKWAY WEST CHESTERFIELD, MISSOURI 63017 – 1732, ESTAD S UNID S DE AMERICA.-

APOSTILLA

(Convención de La Haya del 5 de Octubre de 1961)

1. Distrito de Columbia
   Estados Unidos de América
2. Este documento público ha sido firmado por **MELISSA O. JACKSON**
3. actuando en capacidad de **NOTARIO PÚBLICO EN Y PARA EL DISTRITO DE COLUMBIA**
   MELISSA O. JACKSON, NOTARIO PUBLICO EN Y PARA EL
4. lleva el sello/timbre de **DISTRITO DE COLUMBIA**

CERTIFICADO

5. en Washington, D.C.
6. el 6 de Febrero de 2004
7. por el Secretario del Distrito de Columbia
8. No. 121542
9. Sello/Timbre

10. Firma

(Firma)

SHERRYL H. NEWMAN

En el certificado notarial hay un sello que dice:
ROSALBA OLIVERI
Notario Público, Estado de New York
No. 01OL6085628
Calificado en el Condado de Queens
Certificado presentado en el Condado de New York
La comisión expira el 30 de Diciembre de 2006

Detrás del certificado notarial hay un sello que dice:
CERTIFICO POR EL PRESENTE QUE ESTE
ES EL DOCUMENTO ORIGINAL

Suscrito y jurado ante mí, en mi presencia, este
6 de Febrero de 2004 un Notario Público
en y para el Distrito de Columbia
Melissa O. Jackson
Mi comisión expira el 14 de Diciembre de 2008

MELISSA O. JACKSON

CONSULADO NOTARIO CUARENTA Y SEIS DEL CIRCULO DE BOGOTA, PARA CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
16 JUN 2005
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SEIS

427

REPÚBLICA DE COLOMBIA

GAVIRIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

Datos de la oficina de registro

Clase de oficina:	Registraduría		Notaría	X	Consulado		Corregimiento		Insp. de Policía		Código	9795

País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C NOTARIA 32.

Datos del inscrito

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción										Hora	Número de certificado de defunción
Año	2	0	0	4	Mes	1	0	Día	3	0	04:10 PM	A- 2094375.

Juzgado que profiere la sentencia	Fecha de la sentencia			
	Año	Mes	Día	

Documento presentado				Nombre y cargo del funcionario
Autorización Judicial		Certificado Médico	X	ANDRES DIAZ CAMPOS.- R.M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO H.

Documentos de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	

Primer testigo

Apellidos y nombres completos

Documentos de identificación (Clase y número)	Firma

Segundo testigo

Apellidos y nombres completos

Documentos de identificación (Clase y número)	Firma

Fecha de inscripción										Nombre y firma del funcionario que autoriza
Año	2	0	0	4	Mes	1	1	Día	0	2	BLANCA [illegible] RESTREPO

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO : QUE:

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: ST 62209
que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004

NELSON FLOREZ G.
SECRETARIO DELEGADO

NOTARIA 32 DEL CIRCULO DE BOGOTA D.C.
NELSON FLOREZ G.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1834 DE 1989

420
420

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	(✓)
- Indicación de que se solicita la concesión de una patente.	( )	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
- Descripción de la invención.	( )	(✓)
- Dibujos de ser estos pertinentes. X	( )	(✓)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: Claudia M Nieto C

Fecha:

424
429

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
HECTOR GOMEZ MEJIA
Apoderado
PHARMACIA CORPORATION

Oficio N° . 06601

ASUNTO:	Radicación N°	05-58718
	Solicitud internacional	PCT/US2003/040932
	Fecha inicio fase nacional	21/07/2005
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).
- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 05 AGO 2005.

202030

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia