QF

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO 07-116002

SIC

NOV 17 Organizacion CSA Ltda

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

ENTRADA EN FASE NACIONAL

1. EXPEDIENTE No. 07-116002

4. TITULO DERIVADOS DE PURINA E IMIDAZOPIRIDINA PARA INMUNOSUPRESIÓN

1. CLASIFICACION INTERNACIONAL A61K31/52 // A61P37/06

1. SOLICITANTE PHARMACOPEIA, INC.

DOMICILIO CRANBURY, NEW JERSEY, ESTADOS UNIDOS DE AMÉRICA

4. APODERADO JUAN PABLO CADENA SARMIENTO

2. SANTAFE DE BOGOTA, D.C. 01/11/2007.

FORMA P 10)

Oficina de Comunicaciones

PETITORIO

AS: 105.374

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-116002- -00000-0000
Fecha: 2007-11-01 16:29:37 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 449

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: **PHARMACOPEIA, INC.** Dirección: 3000 Eastpark Blvd., Cranbury, New Jersey 08512, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos de América Lugar de Constitución: Estados Unidos de América Teléfono: Fax: E-mail	**IDENTIFICACIÓN** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21 Torre B – Piso 4, Bogotá, Colombia. Teléfono: 744-2200 Fax: 742-2200 E-mail:	**IDENTIFICACIÓN** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre:** Michael OHLMEYER, Adolph BOHNSTEDT, Celia KINGSBURY, Koc-Kan HO, Jorge QUINTERO, Ming YOU, Haengsoon PARK, Yingchun LU. **Dirección:** 6 Beechtree Lane, Plainsboro, New Jersey 08536, US; 5 Red Fox Street, Burlington, New Jersey 08016, US; 1 Woodland Avenue, Cream Ridge, New Jersey 08514, US; 104 Pheasant Run, Monmouth Junction, New Jersey 08852, US; 7 Van Delft Drive, South Amboy, New Jersey 08879, US; 3 Madison Drive, Plainsboro, New Jersey 08536, US 8910 Tamarron Drive, Plainsboro, New Jersey 08536, US; 91 Stillwell Road, Kendall Park, New Jersey 08824, US (Respectivamente). **Nacionalidad o Domicilio:** Estados Unidos de América (Respectivamente).	

5 PCT (86)

Solicitud Internacional No. PCT/US2006/012824 Fecha 05-04-2006
Publicación Internacional No WO 2006/108103 A1 Fecha 12-10-2006

6 Título (54): DERIVADOS DE PURINA E IMIDAZOPIRIDINA PARA INMUNOSUPRESIÓN

7 Clasificación Internacional (51): A61K31/52 // A61P37/06

8 Prioridad SI ☒ NO ☐

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US	05-04-2005	60/668,286
US	15-11-2005	60/736,663

9 Comprobante de pago No. 07- 72,608 **Fecha** 31-10-2007

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $482.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] 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
  Documentos PCT

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

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

AS. 105374

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 449

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	59040581	10/09/2007	2,430,000.00
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	62762483	10/09/2007	32,280,000.00

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

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

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/US2006/012824 **MODELO DE UTILIDAD** [ ] **DISEÑO INDUSTRIAL** [ ]

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES PHARMACOPEIA, INC.

DOMICILIO CRANBURY, NEW JERSEY, ESTADOS UNIDOS DE AMÉRICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO DERIVADOS DE PURINA E IMIDAZOPIRIDINA PARA INMUNOSUPRESIÓN

CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) MICHAEL OHLMEYER, ADOLPH BOHNSTEDT, CELIA KINGSBURY, KOC-KAN HO,

OTROS JORGE QUINTERO, MING YOU, HAENGSOON PARK, YINGCHUN LU.

OFICINA DE COMUNICACIONES

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

HANSEN, Philip
Heslin Rothenberg Farley & Mesiti P.C.
5 Columbia Circle
Albany, New York 12203
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
07 August 2007 (07.08.2007)

Applicant's or agent's file reference
1073.081BWO

IMPORTANT NOTIFICATION

International application No.
PCT/US2006/012824

International filing date *(day/month/year)*
05 April 2006 (05.04.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
PHARMACOPEIA DRUG DISCOVERY, INC.
3000 Eastpark Blvd.
Cranbury, New Jersey 08512
United States of America

State of Nationality: US
State of Residence: US
Telephone No.: (609) 452-3636
Facsimile No.: (609) 452-3672
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
PHARMACOPEIA, INC.
3000 Eastpark Blvd.
Cranbury, New Jersey 08512
United States of America

State of Nationality: US
State of Residence: US
Telephone No.: (609) 452-3636
Facsimile No.: (609) 452-3672
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
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(71) Applicant *(for all designated States except US)*: **PHARMACOPEIA DRUG DISCOVERY, INC.** [US/US]; 3000 Eastpark Blvd., Cranbury, New Jersey 08512 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **OHLMEYER, Michael** [GB/US]; 6 Beechtree Lane, Plainsboro, New Jersey 08536 (US). **BOHNSTEDT, Adolph** [US/US]; 5 Red Fox Street, Burlington, New Jersey 08016 (US). **KINGSBURY, Celia** [NZ/US]; 1 Woodland Avenue, Cream Ridge, New Jersey 08514 (US). **HO, Koc-Kan** [US/US]; 104 Pheasant Run, Monmouth Junction, New Jersey 08852 (US). **QUINTERO, Jorge** [US/US]; 7 Van Delft Drive, South Amboy, New Jersey 08879 (US). **YOU, Ming** [CN/US]; 3 Madison Drive, Plainsboro, New Jersey 08536 (US). **PARK, Haengsoon** [KR/US]; 8910 Tamarron Drive, Plainsboro, New Jersey 08536 (US). **LU, Yingchun** [CN/US]; 91 Stillwell Road, Kendall Park, New Jersey 08824 (US).

(74) Agents: **HANSEN, Philip** et al.; Heslin Rothenberg Farley & Mesiti P.C., 5 Columbia Circle, Albany, New York 12203 (US).

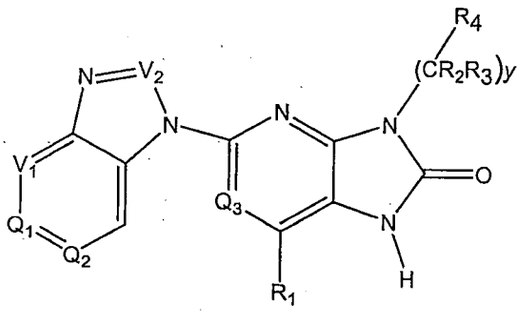
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR; BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC,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

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

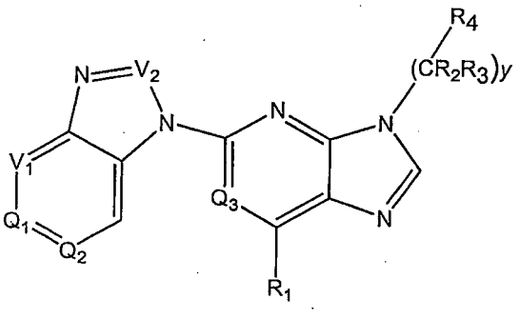
Published:
— *with international search report*

[Continued on next page]

(54) Title: PURINE AND IMIDAZOPYRIDINE DERIVATIVES FOR IMMUNOSUPPRESSION



(I)



(II)

(57) Abstract: The present invention provides novel purine and imidazopyridine derivatives useful for the prevention and treatment of autoimmune diseases, inflammatory disease, mast cell mediated disease and transplant rejection. The compounds are of the general formulas (I) and (II).

WO 2006/108103 A1

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

PURINE AND IMIDAZOPYRIDINE DERIVATIVES FOR IMMUNOSUPPRESSION

FIELD OF THE INVENTION

[0001] The invention relates to purine and imidazopyridine derivatives useful as immunosuppressants.

BACKGROUND OF THE INVENTION

[0002] Immunosuppression is an important clinical approach in treating autoimmune disease and in preventing organ and tissue rejection. The clinically available immunosuppressants, including azathioprine, cyclosporine and tacrolimus, although effective, often cause undesirable side effects including nephrotoxicity, hypertension, gastrointestinal disturbances and gum inflammation. Inhibitors of the tyrosine kinase Jak3 are known to be useful as immunosuppressants (see US patent 6,313,129).

[0003] The members of the Janus kinase (Jak) family of non-receptor intracellular tyrosine kinases are components of cytokine signal transduction. Four family members have been identified to date: Jak1, Jak2, Jak3 and Tyk2. The Jaks play a key role in the intracellular signaling mediated through cytokine receptors. Upon binding of cytokines to their receptors, Jaks are activated and phosphorylate the receptors, creating docking sites for other signaling molecules, in particular members of the signal transducer and activator of transcription (STAT) family. While expression of Jak1, Jak2 and Tyk2 is relatively ubiquitous, Jak3 expression is temporally and spatially regulated. Jak3 is predominantly expressed in cells of hematopoietic lineage; it is constitutively expressed in natural killer (NK) cells and thymocytes and is inducible in T cells, B cells and myeloid cells (reviewed in Ortmann, et al., 1999 and Yamaoka, et al., 2004). Jak3 is also is expressed in mast cells, and its enzymatic activity is enhanced by IgE receptor/FcεRI cross-linking (Malaviya and Uckun, 1999).

[0004] A specific, orally active Jak3 inhibitor, CP-690,550, has been shown to act as an effective immunosuppressant and prolong animal survival in a murine model of heart transplantation and a primate model of kidney transplantation (Changelian, et al., 2003).

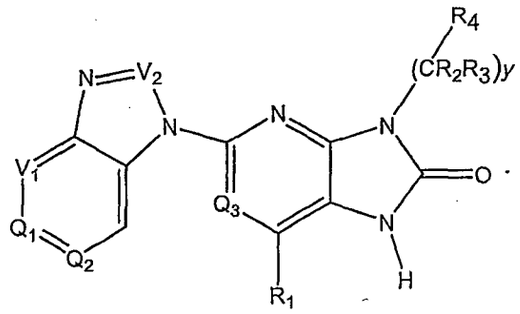
[0005] Furthermore, aberrant Jak3 activity has been linked to a leukemic form of cutaneous T-cell lymphoma (Sezary's syndrome) and acute lymphoblastic leukemia (ALL), the most common form of childhood cancer. The identification of Jak3 inhibitors has provided the basis for new clinical approaches in treating leukemias and lymphomas (Cetkovic-Cvrlje, Marina; Uckun, Faith M., Targeting Janus Kinase 3 in the treatment of Leukemia and Inflammatory Diseases. Archivum Immunologiae et Therapie Experimentalis (2004) and/or Uckun, Faith M.; Mao, Chen. Tyrosine kinases as new molecular targets in treatment treatment of inflammatory disorders and leukemia. Current Parmaceutical Design(2004)). Two dimethoxyquinazoline derivatives, WHI-P131 (JANEX-1) and WHI-P154 (JANEX-2), have been reported to be selective inhibitors of Jak3 in leukemia cells (Sudbeck et al., 1999).

[0006] Jak3 has also been shown to play a role in mast-cell mediated allergic reactions and inflammatory diseases and serves as a target in indications such as asthma and anaphylaxis.

[0007] Therefore, compounds that inhibit Jak3 are useful for indications such as leukemias and lymphomas, organ and bone marrow transplant rejection, mast cell-mediated allergic reactions and inflammatory diseases and disorders.

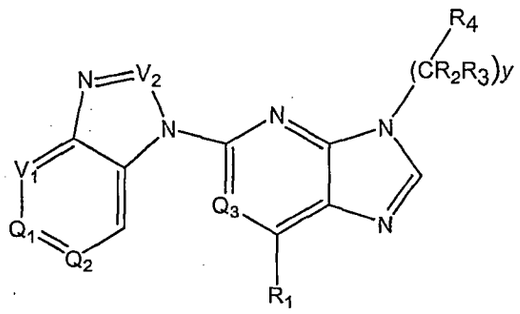
SUMMARY OF THE INVENTION

[0008] It has now been found that compounds of general formula **I** and **II** are potent and selective inhibitors of Jak3:



I

and



II

[0009] In these compounds,

Q_1 and Q_2 are independently selected from the group consisting of CX_1, CX_2, and nitrogen;

Q_3 is N or CH;

X_1 and X_2 are independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, cyano, halo, halo$(C_1$-$C_6)$alkyl, hydroxyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, nitro, carboxamido, and methylsulfonyl;

V_1 and V_2 are independently selected from CH and N;

R_1 is selected from the group consisting of hydrogen and methyl;

y is zero or an integer selected from 1, 2 and 3;

R_2 and R_3 are selected independently for each occurrence of (CR_2R_3) from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl; and

R_4 is selected from a group consisting of alkyl, heterocyclyl, aryl, substituted alkyl, substituted heterocyclyl, and substituted aryl.

[0010] The members of these genera are useful in inhibiting Jak3 activity and as such are useful in indications where clinical immunosuppression is desired and in the treatment of hematological cancers.

[0011] In another aspect, the invention relates to pharmaceutical compositions comprising a therapeutically effective amount of at least one compound of general formula **I** or general formula **II**, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[0012] In another aspect, the invention relates to a method for treating a disease by altering a response mediated by Jak3 tyrosine kinase. The method comprises bringing into contact with Jak3 at least one compound of general formula **I** or **II**.

[0013] In yet another aspect the present invention relates to a method of suppressing the immune system in a subject in need thereof comprising administering to the subject a therapeutically effective amount of at least one compound of general formula **I** or **II**.

[0014] Suppression of immune system activity is desirable for preventing or treating tissue or organ rejection following transplant surgery and for preventing and treating diseases and disorders arising from aberrant activity of the immune system, in particular autoimmune disorders and diseases. Exemplary autoimmune disorders include graft versus host disease (GVHD), insulin-dependent diabetes (Type I), Hashimoto's thyroiditis and Graves' disease, pernicious anemia, Addison's disease, chronic active hepatitis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, scleroderma and myasthenia gravis.

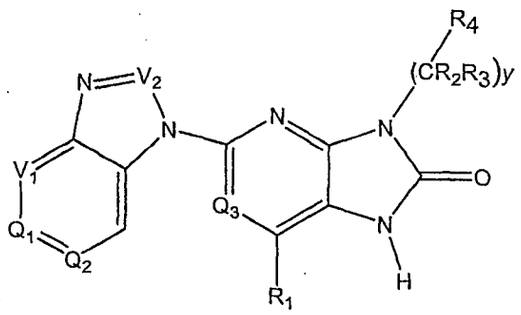
[0015] The compounds of the present invention are useful in preventing and treating diseases and disorders related to mast cell-mediated allergic reactions and inflammation.

[0016] Other indications in which the Jak3 inhibitors are useful include leukemias and lymphomas.

DETAILED DESCRIPTION OF THE INVENTION

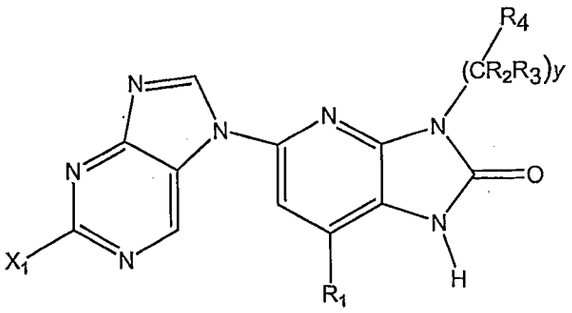
[0017] Throughout this specification the substituents are defined when introduced and retain their definitions.

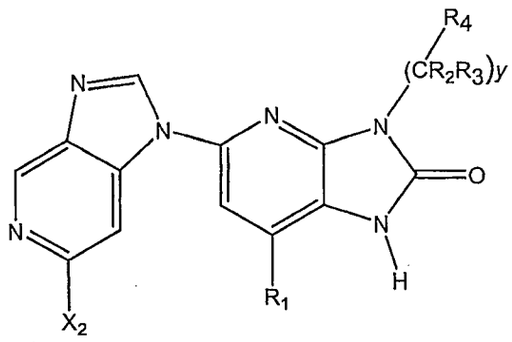
[0018] In a first aspect the invention relates to purinones and imidazopyridinones having general formula **I**:

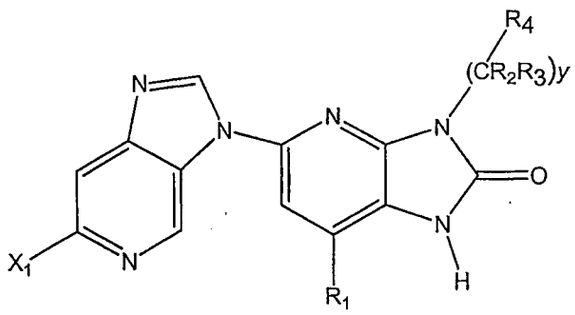


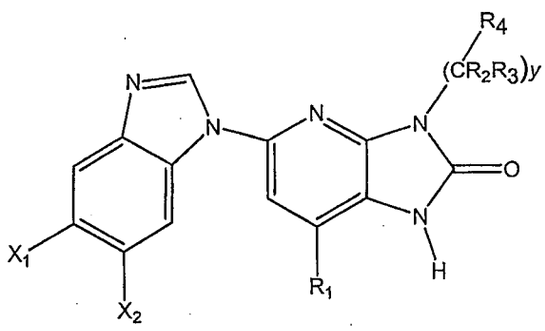
I

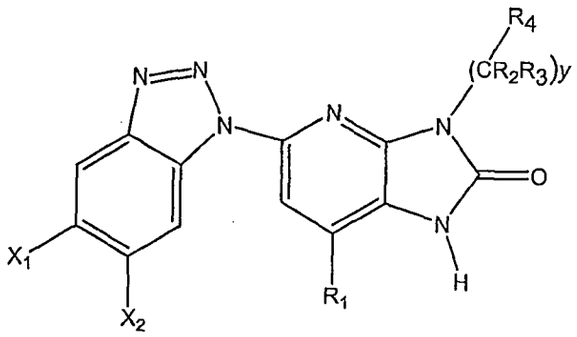
[0019] The members of the genus **I** may be conveniently divided into subgenera based on the values of Q and V. When Q_1 is carbon, Q_2 is nitrogen, V_1 is nitrogen, and V_2 is carbon a subgenus of purinones and imidazo[4,5-b]pyridinones having an attached purine arises. When Q_1 is carbon, Q_2 is nitrogen, and both V_1 and V_2 are carbon, a subgenus of purinones and imidazo[4,5-b]pyridinones having an attached imidazo[5,4-c]pyridine arises. When Q_1 and Q_2 are carbon, and both V_1 and V_2 are carbon, a subgenus of purinones and imidazo[4,5-b]pyridinones having an attached benzimidazole arises. When Q_1 and Q_2 are carbon, V_1 is carbon, and V_2 is nitrogen, a subgenus of purinones and imidazo[4,5-b]pyridinones having an attached benzotriazole arises. The genus could similarly be divided on the basis of Q_3. When Q_3 is nitrogen, a subgenus of purinones having an attached purine, imidazo[5,4-c]pyridine, benzimidazole or benzotriazole arises. When Q_3 is carbon, a subgenus of imidazo[4,5-b]pyridinones having an attached purine, imidazo[5,4-c]pyridine, benzimidazole or benzotriazole arises. The structures of these subgenera are shown below:



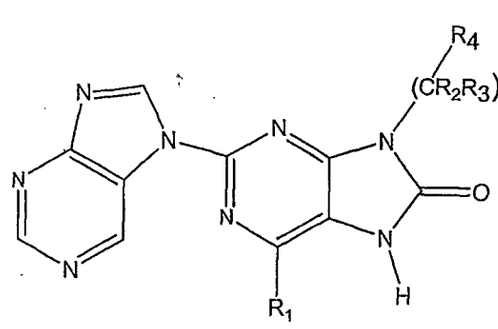


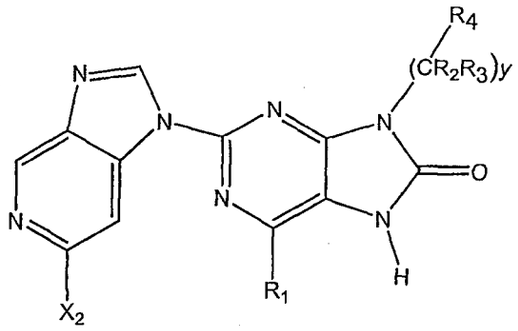


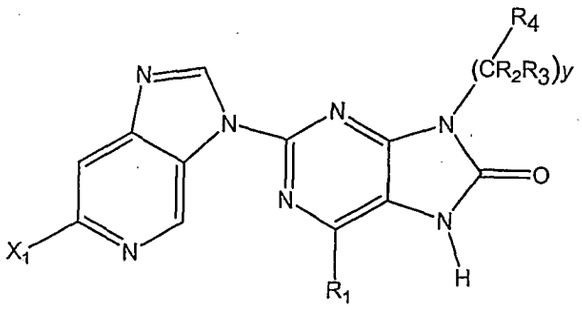


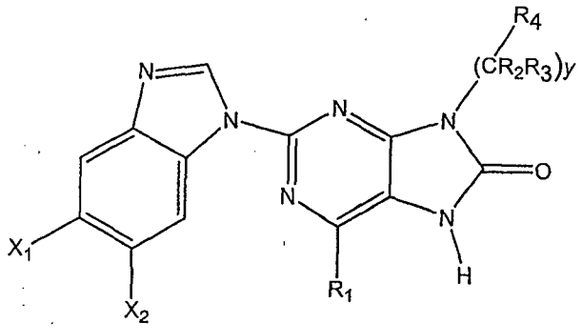


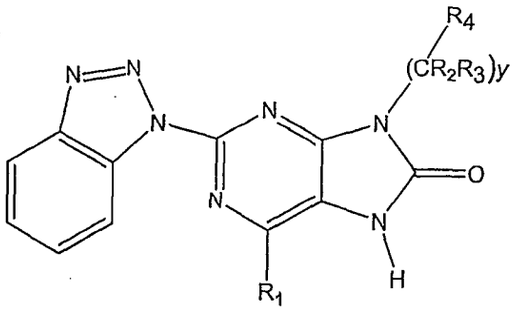
[0020] When Q_3 is nitrogen, a subgenus of purinones having an attached purine, imidazo[5,4-c]pyridine, benzimidazole or benzotriazole arises. The structures of these subgenera are shown below

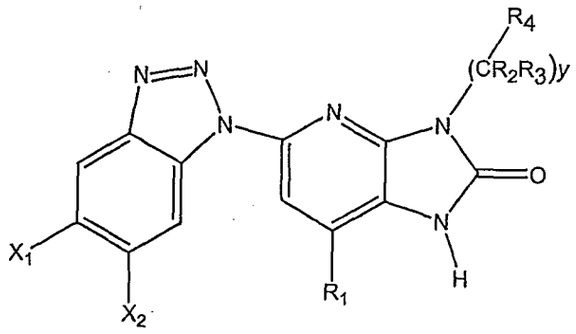




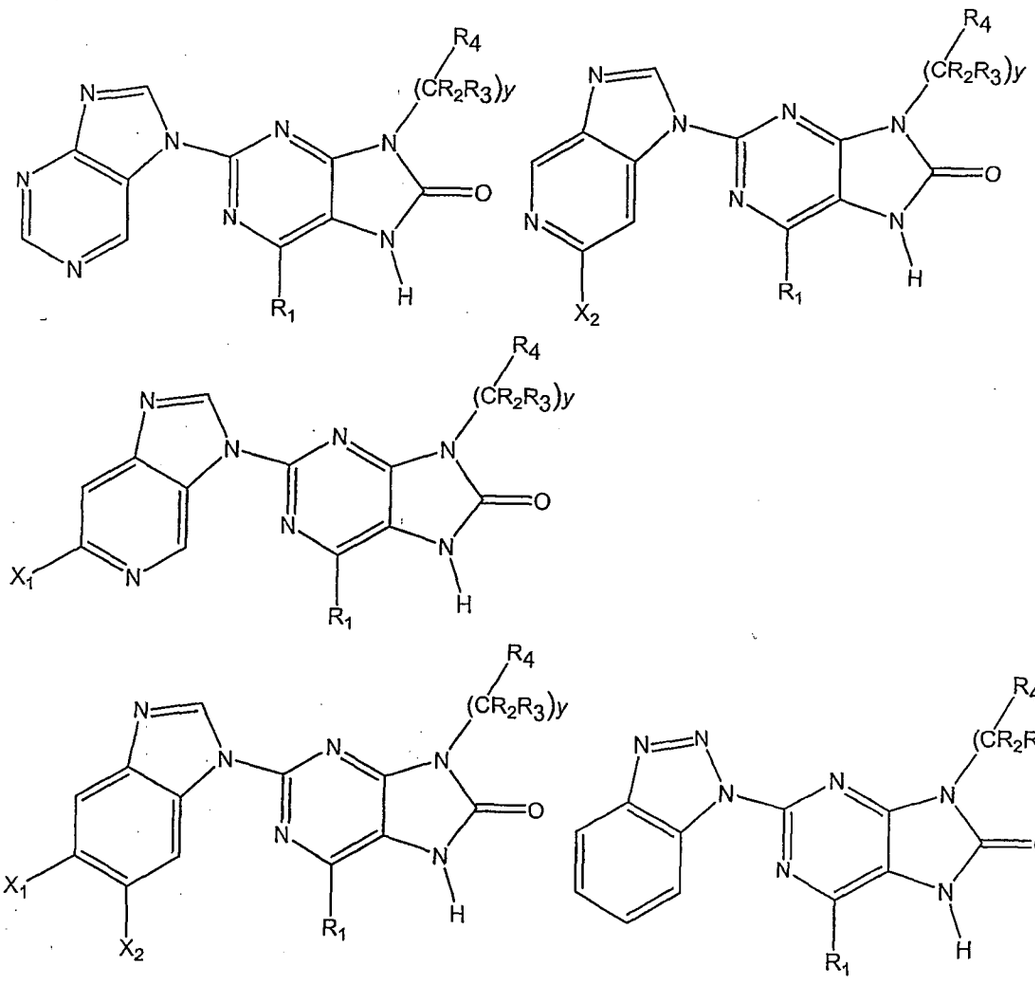




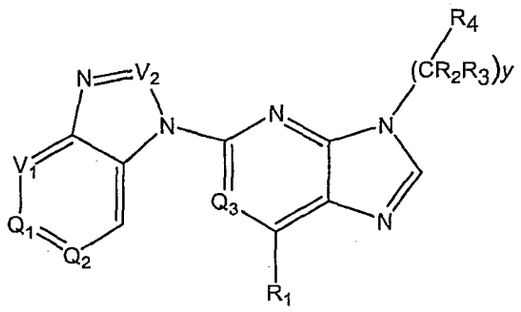




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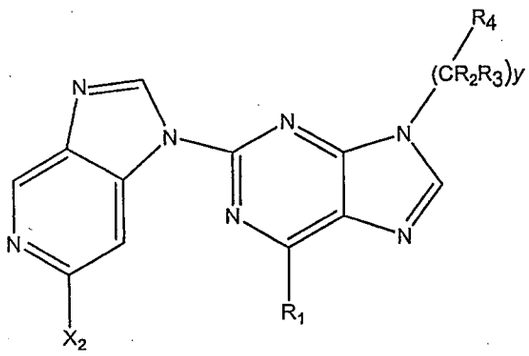


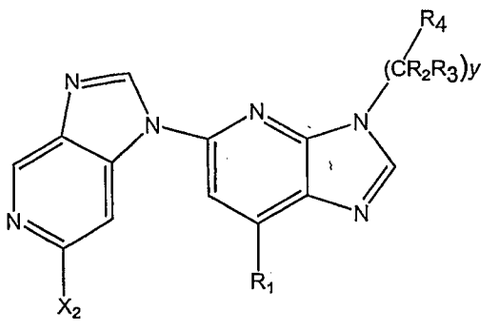
[0021] In another aspect the invention relates to purines and imidazopyridines having general formula **II**:

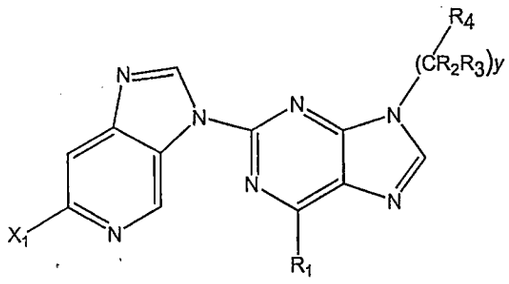


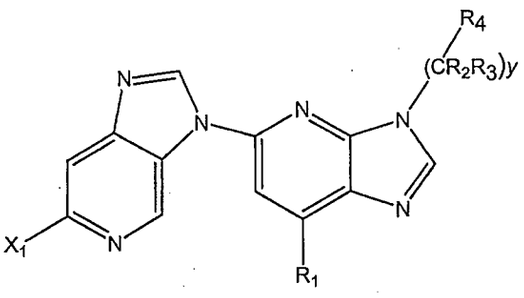
II

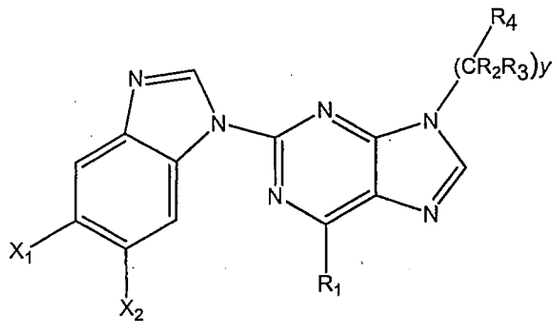
[0022] The members of the genus **II** may be similarly divided into subgenera based on the values of Q and V. When Q_1 is carbon, Q_2 is nitrogen, V_1 is nitrogen, and V_2 is carbon, a subgenus of purines and imidazo[4,5-b]pyridines having an attached purine arises. When Q_1 is carbon, Q_2 is nitrogen, and both V_1 and V_2 are carbon, a subgenus of purines and imidazo[4,5-b]pyridines having an attached imidazo[5,4-c]pyridine arises. When all of Q_1, Q_2, V_1 and V_2 are carbon, a subgenus of purines and imidazo[4,5-b]pyridines having an attached benzimidazole arises. When Q_1, Q_2 and V_1 are carbon, and V_2 is nitrogen, a subgenus of purines and imidazo[4,5-b]pyridines having an attached benzotriazole arises. The genus could similarly be divided on the basis of Q_3. When Q_3 is nitrogen, a subgenus of purines having an attached purine, imidazo[5,4-c]pyridine, benzimidazole or benzotriazole arises. When Q_3 is carbon, a subgenus of imidazo[4,5-b]pyridines having an attached purine, imidazo[5,4-c]pyridine, benzimidazole or benzotriazole arises. The structures of these subgenera are shown below:

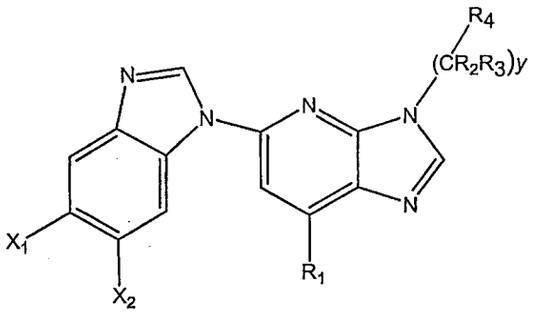


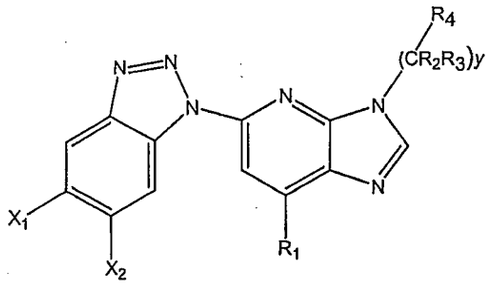


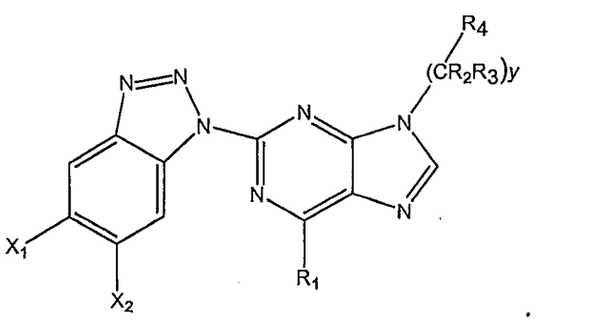


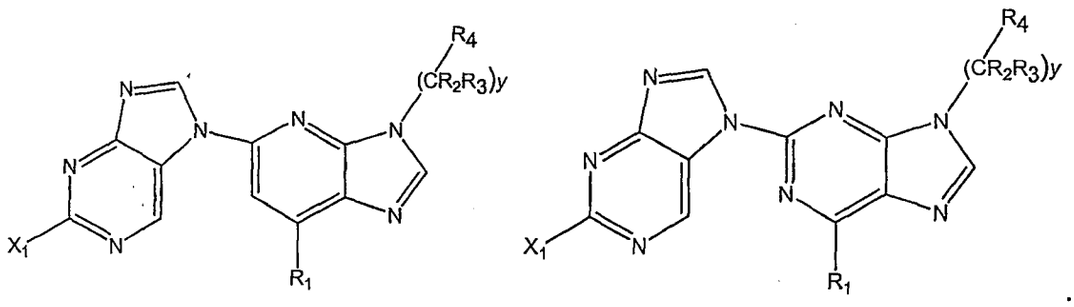








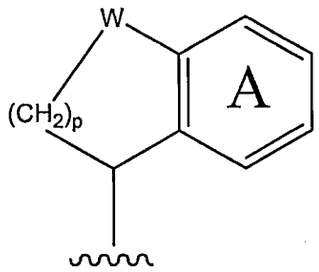




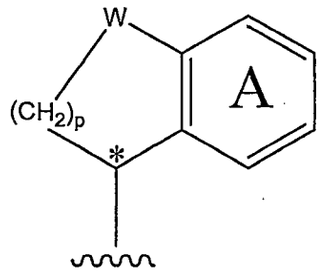
[0023] In certain embodiments, X_1 and X_2 are selected from hydrogen, cyano, chloro, fluoro, trifluoromethyl, trifluoromethoxy, carboxamido, and methyl; in other embodiments R_1 is H. In one subdivision, y is zero; in another y is 1 or 2 and R_2 and R_3 are hydrogen or methyl. Examples of R_4 include: cyclopentyl, cyclohexyl, piperidine, oxepane, benzoxepane, dihydrocyclopentapyridine, phenyl, tetralin, indane, tetrahydropyran, tetrahydrofuran, tetrahydroindole, isoquinoline, tetrahydroisoquinoline, quinoline, tetrahydroquinoline, chroman, isochroman, pyridine, pyrazine, pyrimidine, dihydropyran, dihydrobenzofuran, tetrahydrobenzofuran, tetrahydrobenzothiophene, furan, dihydropyrano[2,3-b]pyridine (see example below), tetrahydroquinoxaline, tetrahydrothiopyran (thiane), thiochroman (dihydrobenzothiin), thiochroman-1,1-dioxide, tetrahydronaphthalene, oxabicyclooctane, oxocane, tetrathiohydropyran-1,1-dioxide, tetrathiohydropyranoxide, or any of the foregoing rings carrying from 1-3 additional substituents, such as halogen, methyl, methoxy, trifluoromethyl, cyano, hydroxy, oxo, oxide and acetyl. Additional examples in which R_4 is alkyl or substituted alkyl include subgenera in which R_4 is oxaalkyl (alkoxyalkyl).

[0024] In certain embodiments of genus **I**, y is 1 or 2; R_2 and R_3 are hydrogen or methyl and R_4 is phenyl, quinoline, pyridine, pyrazine or substituted phenyl, quinoline, pyridine or pyrazine. In other embodiments of genus **I**, y is zero and R_4 is cyclopentyl, cyclohexyl, phenyl, piperidine, oxepane, benzoxepane, dihydrocyclopentapyridine, tetralin, indane, tetrahydropyran, tetrahydrofuran, tetrahydroindole, isoquinoline, tetrahydroisoquinoline, quinoline, tetrahydroquinoline, chroman, pyridine, pyrimidine, dihydropyran, dihydrobenzofuran, tetrahydrobenzofuran, tetrahydrobenzothiophene, dihydrobenzothiophene, furan, dihydropyrano[2,3-b]pyridine, tetrahydroquinoxaline,

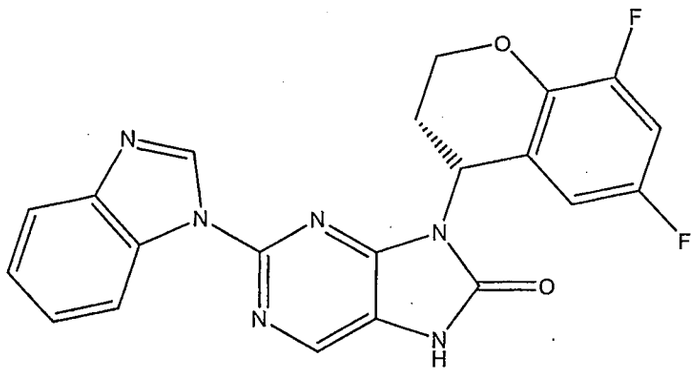
tetrahydrothiopyran (thiane), thiochroman (dihydrobenzothiin), thiochroman-1,1-dioxide, tetrahydronaphthalene, oxabicyclooctane, oxocane, tetrathiohydropyran-1,1-dioxide, tetrathiohydropyranoxide, or a substituted ring from the foregoing list. In further embodiments, (a) y is zero and R_4 is selected from cyclopentyl, cyclohexyl, oxepane, dihydrocyclopentapyridine, tetrahydropyran, tetrahydroquinoline, chroman, dihydrobenzofuran, tetrahydrobenzofuran, dihydropyrano[2,3-b]pyridine and tetrahydroquinoxaline, each optionally substituted with hydroxy, oxo, or halogen; or (b) y is 1 or 2, R_2 and R_3 are hydrogen or methyl and R_4 is selected from phenyl, pyridine and pyrazine, each optionally substituted with halogen. When y is zero, R_4 may be tetrahydropyran-4-yl, 4-hydroxycyclohexyl, 4-oxocyclohexyl, oxepan-4-yl, chroman-4-yl or fluoro substituted chroman-4-yl. It appears that, although both enantiomers are active, compounds in which the carbon at 4 of the chroman is of the (R) configuration have higher potency. Certain of the foregoing subgenera in which y is zero may also be described by a representation in which R_4 is



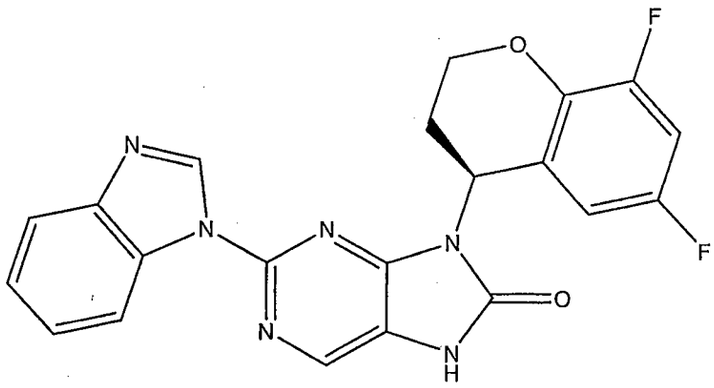
[0025] According to this representation, W is CH_2, C=O, CHOH, or O; p is 1, 2 or 3; and A is a six-membered heteroaromatic ring containing 1 or 2 nitrogens, a benzene ring optionally substituted with one or two fluorines, or a five-membered heterocyclic ring. The wavy line denotes the point of attachment to the purinone. Examples in which W is C=O include indanones, tetralones and benzosuberones. Examples in which W is CH_2 include indanes, tetralins and benzocycloheptanes. Examples in which W is CHOH include substituted tetralins. Examples in which W is O include dihydrobenzofuran, chroman, benzopyrans and benzoxepanes. As before, compounds in which the carbon marked with an asterisk



is of the (R) configuration appear to be more potent than their corresponding (S) enantiomers. An example of such a compound is



which is more potent than its corresponding (S) enantiomer



,

but both exhibit Jak3 kinase IC_{50} below 1 micromolar. Examples below also include compounds in which y is 1 and R_4 is selected from difluorophenyl, fluorophenyl, chlorophenyl, chlorofluorophenyl, pyridin-3-yl and pyrazin-3-yl.

[0026] In certain embodiments of genus **II**, nitrogen is present at the 7 and 9 position on the 6,5 bicyclic heterocycle; X_1 is selected from hydrogen, cyano and fluoro; Q_1 is N and R_1 is H. In some embodiments, y is zero and R_4 is selected from phenyl, tetrahydropyran (e.g. tetrahydropyran-4-yl), isoquinoline (e.g. isoquinolin-8-yl), tetrahydroquinoline (e.g.

1,2,3,4-tetrahydroquinolin-5-yl), and their substituted counterparts. In other embodiments, y is 1 and R_4 is selected from difluorophenyl, fluorophenyl, chlorophenyl, chlorofluorophenyl, pyridin-3-yl and pyrazin-3-yl.

[0027] All of the compounds falling within the foregoing parent genera and their subgenera are useful as Jak3 inhibitors.

Definitions

[0028] For convenience and clarity certain terms employed in the specification, examples and claims are described herein.

[0029] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. Lower alkyl refers to alkyl groups of from 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-and t-butyl and the like. Preferred alkyl groups are those of C_{20} or below; more preferred are C_1-C_8 alkyl. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, or other bridged systems and the like.

[0030] C_1 to C_{20} hydrocarbon includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl.

[0031] Alkoxy or alkoxyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons. Oxaalkyl refers to alkyl residues in which one or more carbons (and their associated hydrogens) have been replaced by oxygen. Examples include methoxypropoxy, 3,6,9-trioxadecyl and the like. The term oxaalkyl is intended as it is understood in the art [see Naming and Indexing of Chemical Substances for Chemical Abstracts, published by the American Chemical Society, ¶196, but without the restriction of ¶127(a)], i.e. it refers to compounds in which the oxygen is bonded via a single bond

to its adjacent atoms (forming ether bonds); it does not refer to doubly bonded oxygen, as would be found in carbonyl groups.

[0032] Acyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, t-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

[0033] Aryl and heteroaryl mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-3 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S; or a tricyclic 13- or 14-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S. The aromatic 6- to 14-membered carbocyclic rings include, e.g., benzene and naphthalene, and for the purposes of the present invention, fused moieties such as tetrahydronaphthalene (tetralin), and indane, in which one or more rings are aromatic, but not all need be. The 5- to 10-membered aromatic heterocyclic rings include, e.g., imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

[0034] Arylalkyl refers to a substituent in which an aryl residue is attached to the parent structure through alkyl. Examples are benzyl, phenethyl and the like. Heteroarylalkyl refers to a substituent in which a heteroaryl residue is attached to the parent structure through alkyl. Examples include, e.g., pyridinylmethyl, pyrimidinylethyl and the like.

[0035] Heterocycle means a cycloalkyl or aryl residue in which from one to three carbons is replaced by a heteroatom selected from the group consisting of N, O and S. The nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Examples of heterocycles include pyrrolidine, pyrazole, pyrrole, indole, quinoline, isoquinoline, tetrahydroisoquinoline,

benzofuran, benzodioxan, benzodioxole (commonly referred to as methylenedioxyphenyl, when occurring as a substituent), tetrazole, morpholine, thiazole, pyrazine, pyridine, pyridazine, pyrimidine, thiophene, furan, oxazole, oxazoline, isoxazole, dioxane, tetrahydrofuran and the like. Further examples include cyclic ethers (including bridged cyclic ethers), lactones, lactams, cyclic ureas, and the like. It is to be noted that heteroaryl is a subset of heterocycle in which the heterocycle is aromatic. Examples of heterocyclyl residues additionally include piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxo-pyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinylsulfoxide, thiamorpholinylsulfone, oxadiazolyl, triazolyl and tetrahydroquinolinyl. A nitrogenous heterocycle is a heterocycle containing at least one nitrogen in the ring; it may contain additional nitrogens, as well as other heteroatoms. The nitrogenous heterocycle may be monocyclic, bicyclic, or multi-cyclic.

[0036] Substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein up to three H atoms in each residue are replaced with halogen, haloalkyl, hydroxy, loweralkoxy, hydroxyloweralkyl, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone, acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzenesulfonyl, benzyloxy, or heteroaryloxy. When the parent is a heterocycle that allows such substitution, the term also includes oxides, for example pyridine-N-oxide, thiopyran sulfoxide and thiopyran-S,S-dioxide. As mentioned above, two hydrogens on a single carbon may be replaced by a carbonyl to form an oxo derivative. Noteworthy oxo-substituted aryl residues include tetralone (3,4-dihydronaphthalen-1(2*H*)-one) and indanone (2,3-dihydroinden-1-one).

[0037] The terms "halogen" and "halo" refer to fluorine, chlorine, bromine or iodine.

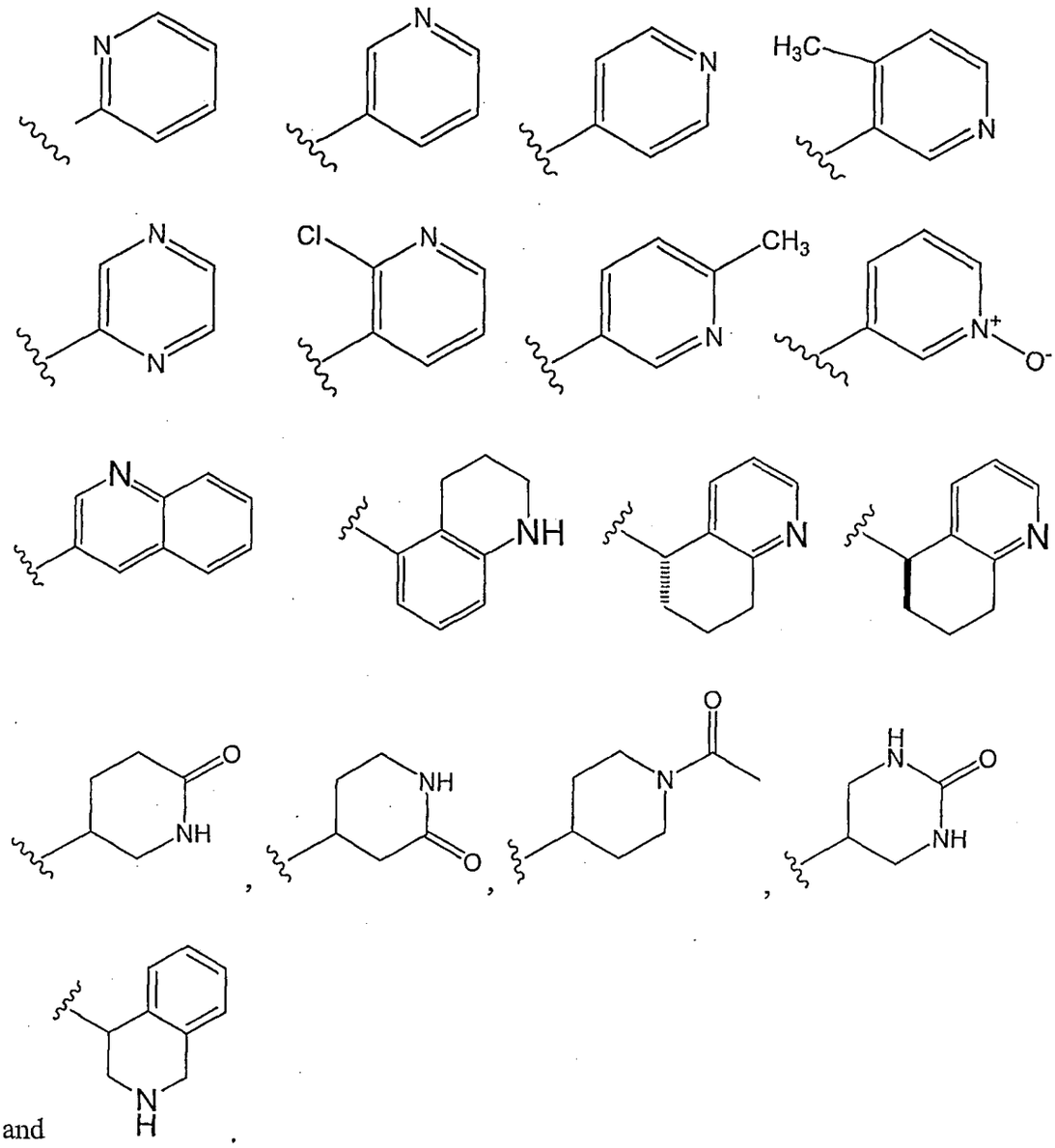
[0038] Some of the compounds described herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric

forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration; thus a carbon-carbon double bond depicted arbitrarily herein as trans may be Z, E or a mixture of the two in any proportion.

[0039] It will be recognized that the compounds of this invention can exist in radiolabeled form, i.e., the compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine, chlorine and iodine include ^{3}H, ^{14}C, ^{35}S, ^{18}F, ^{36}Cl and ^{125}I, respectively. Compounds that contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Tritiated, i.e. ^{3}H, and carbon-14, i.e., ^{14}C, radioisotopes are particularly preferred for their ease in preparation and detectability. Radiolabeled compounds of this invention can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabeled compounds can be prepared by carrying out the procedures disclosed in the Examples by substituting a readily available radiolabeled reagent for a non-radiolabeled reagent. Because of the high affinity for the JAK3 enzyme active site, radiolabeled compounds of the invention are useful for JAK3 assays.

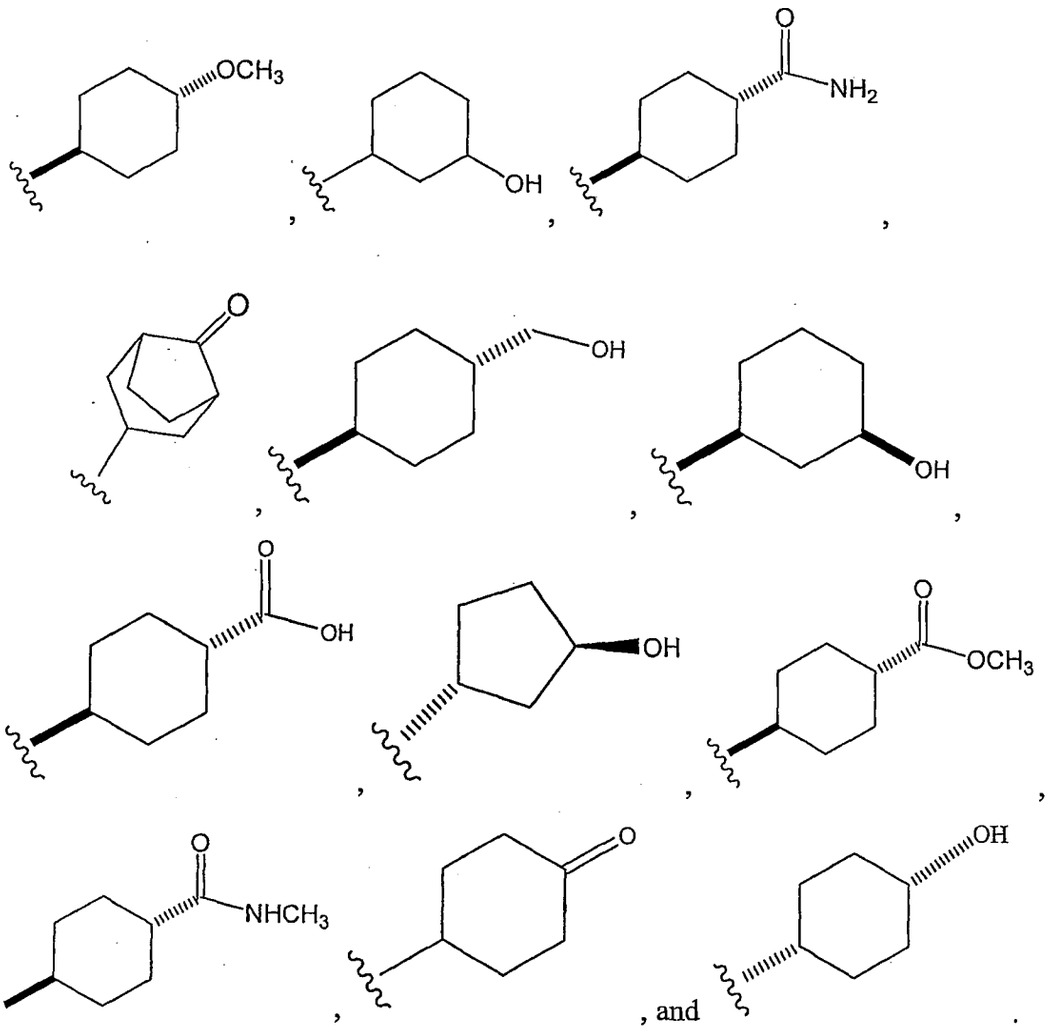
[0040] In one embodiment, R_4 is a heterocycle selected from a nitrogenous heterocycle and an oxygenous heterocycle. Nitrogenous heterocycles that appear in the examples are monocyclic and bicyclic heterocycles or monocyclic and bicyclic heterocycles substituted with one or two substitutions. When y is not zero, heteroaryl is a preferred subset of heterocyclyl for R_4. Exemplary nitrogenous heterocycles include piperidine, pyridine,

pyrazine, pyrimidine, pyridine, quinoline, isoquinoline, tetrahydroquinoline, tetrahydroisoquinoline, and their variously substituted derivatives, such as



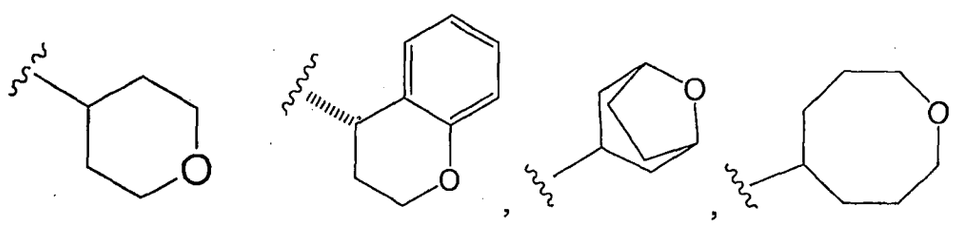
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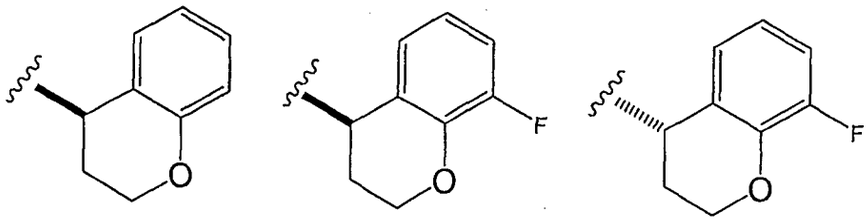
[0041] In another embodiment, R_4 is a substituted cycloalkyl. Substituents include hydroxyl, alkoxy, hydroxyalkyl, oxo, carboxamido (aminocarbonyl), carboxy, and carboalkoxy. Substituted cycloalkyls include:



, and .

[0042] An oxygenous heterocycle is a heterocycle containing at least one oxygen in the ring; it may contain additional oxygens, as well as other heteroatoms. Exemplary oxygenous heterocycles include tetrahydropyran, chroman, pyran, oxocane and their variously substituted derivatives, such as:





Chemical Synthesis

[0043] Terminology related to "protecting", "deprotecting" and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes that involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes of the invention, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups". Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Protective Groups in Organic Synthesis by T.W. Greene [John Wiley & Sons, New York, 1991], which is incorporated herein by reference.

[0044] A comprehensive list of abbreviations utilized by organic chemists appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations", is incorporated herein by reference.

[0045] In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are in themselves known, but are not mentioned here. The starting

materials, for example in the case of suitably substituted benzimidazole ring compounds, are either commercially available, synthesized as described in the examples or may be obtained by the methods well known to persons of skill in the art

[0046] The present invention further provides pharmaceutical compositions comprising as active agents, the compounds described herein.

[0047] As used herein a "pharmaceutical composition" refers to a preparation of one or more of the compounds described herein, or physiologically acceptable salts or solvents thereof, with other chemical components such as physiologically suitable carriers and excipients.

[0048] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations which, can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0049] Compounds that inhibit Jak-3 can be formulated as pharmaceutical compositions and administered to a mammalian subject, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical, transdermal or subcutaneous routes.

[0050] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose,

hydroxypropylmethyl-cellulose, sodium carbomethylcellulose; and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar or alginic acid or a salt thereof such as sodium alginate.

[0051] In addition, enteric coating may be useful as it is may be desirable to prevent exposure of the compounds of the invention to the gastric environment.

[0052] Pharmaceutical compositions, which can be used orally, include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and, optionally, stabilizers.

[0053] In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

[0054] For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's or Ringer's solution or physiological saline buffer. For transmucosal and transdermal administration, penetrants appropriate to the barrier to be permeated may be used in the composition. Such penetrants, including for example DMSO or polyethylene glycol, are known in the art.

[0055] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer with the use of a suitable propellant, e. g., dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e. g., gelatin

for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0056] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active ingredients in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acids esters such as ethyl oleate, triglycerides or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. Optionally, the suspension may also contain suitable stabilizers or agents, which increase the solubility of the compounds, to allow for the preparation of highly concentrated solutions.

[0057] The compounds of the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

[0058] Depending on the severity and responsiveness of the condition to be treated, dosing can also be a single administration of a slow release composition, with course of treatment lasting from several days to several weeks or until cure is effected or diminution of the disease state is achieved. The amount of a composition to be administered will, of course, be dependent on many factors including the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician. The compounds of the invention may be administered orally or via injection at a dose from 0.001 to 2500 mg/kg per day. The dose range for adult humans is generally from 0.005 mg to 10 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and

sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

[0059] As used herein, and as would be understood by the person of skill in the art, the recitation of "a compound" is intended to include salts, solvates and inclusion complexes of that compound. The term "solvate" refers to a compound of Formula **I** or **II** in the solid state, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent for therapeutic administration is physiologically tolerable at the dosage administered. Examples of suitable solvents for therapeutic administration are ethanol and water. When water is the solvent, the solvate is referred to as a hydrate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions. Inclusion complexes are described in Remington: The Science and Practice of Pharmacy 19th Ed. (1995) volume 1, page 176-177, which is incorporated herein by reference. The most commonly employed inclusion complexes are those with cyclodextrins, and all cyclodextrin complexes, natural and synthetic, are specifically encompassed within the claims.

[0060] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. When the compounds of the present invention are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compounds of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, and the like. When the compounds contain an acidic side chain, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-

dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

[0061] The term "preventing" as used herein refers to administering a medicament beforehand to forestall or obtund an attack. The person of ordinary skill in the medical art (to which the present method claims are directed) recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or seriousness of a condition, and this is the sense intended herein.

[0062] It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0063] The compositions may be presented in a packaging device or dispenser, which may contain one or more unit dosage forms containing the active ingredient. Examples of a packaging device include metal or plastic foil, such as a blister pack and a nebulizer for inhalation. The packaging device or dispenser may be accompanied by instructions for administration. Compositions comprising a compound of the present invention formulated in a compatible pharmaceutical carrier may also be placed in an appropriate container and labeled for treatment of an indicated condition.

Indications

[0064] The compounds of the present invention are useful in inhibiting the activity if Jak3 or in inhibiting Jak3 mediated activity and are useful as immunosuppressive agents for tissue and organ transplants, including bone marrow and kidney transplant, and in the treatment of autoimmune and inflammatory diseases and of complications arising therefrom.

[0065] Hyperacute, acute and chronic organ transplant rejection may be treated. Hyperacute rejection occurs within minutes of transplantation. Acute rejection generally occurs within six to twelve months of the transplant. Hyperacute and acute rejections are

typically reversible where treated with immunosuppressant agents. Chronic rejection, characterized by gradual loss of organ function, is an ongoing concern for transplant recipients because it can occur anytime after transplantation.

[0066] There are about 75 different autoimmune disorders known that may be classified into two types, organ-specific (directed mainly at one organ) and non-organ-specific (affecting multiple organs).

[0067] Examples of organ-specific autoimmune disorders are insulin-dependent diabetes (Type I) which affects the pancreas, Hashimoto's thyroiditis and Graves' disease which affect the thyroid gland, pernicious anemia which affects the stomach, Cushing's disease and Addison's disease which affect the adrenal glands, chronic active hepatitis which affects the liver; polycystic ovary syndrome (PCOS), celiac disease, psoriasis, inflammatory bowel disease (IBD) and ankylosing spondylitis.

[0068] Examples of non-organ-specific autoimmune disorders are rheumatoid arthritis, multiple sclerosis, systemic lupus and myasthenia gravis.

[0069] Type I diabetes ensues from the selective aggression of autoreactive T-cells against insulin secreting β cells of the islets of Langerhans. Targeting Jak3 in this disease is based on the observation that multiple cytokines that signal through the Jak pathway are known to participate in the T-cell mediated autoimmune destruction of β cells. Indeed, a Jak3 inhibitor, JANEX-1 was shown to prevent spontaneous autoimmune diabetes development in the NOD mouse model of type I diabetes.

[0070] Graft-versus-host disease (GVHD) is a donor T-cell initiated pathological condition that frequently follows allogeneic bone marrow transplantation (BMT). Substantial experimental and clinical research have demonstrated that donor T-cells are the principal mediators and effectors of GVHD. Jak3 plays a key role in the induction of GVHD and treatment with a Jak3 inhibitor, JANEX-1, was shown to attenuate the severity of GVHD (reviewed in Cetkovic-Cvrlje and Ucken, 2004).

[0071] Mast cells express Jak3 and Jak3 is a key regulator of the IgE mediated mast cell responses including the release of inflammatory mediators. Jak3 was shown to be a valid target in the treatment of mast cell mediated allergic reaction.

[0072] Allergic disorders associated with mast cell activation include Type I immediate hypersensitivity reactions such as allergic rhinitis (hay fever), allergic urticaria (hives), angioedema, allergic asthma and anaphylaxis, i.e., "anaphylatic shock." These disorders are treated or prevented by inhibition of Jak3 activity, for example, by administration of a Jak3 inhibitor according to the present invention.

[0073] According to the present invention, the Jak3 inhibitors may be administered prophylactically, i.e., prior to onset of acute allergic reaction, or they may be administered after onset of the reaction, or at both times.

[0074] Inflammation of tissues and organs occurs in a wide range of disorders and diseases and in certain variations, results from activation of the cytokine family of receptors. Exemplary inflammatory disorders associated with activation of Jak3 include, in a non-limiting manner, skin inflammation due radiation exposure, asthma, allergic inflammation and chronic inflammation such as keratoconjunctivitis sicca.

[0075] The compounds of the present invention are also useful in treating certain malignancies, including skin cancer and hematological malignancy such as lymphomas and leukemias. An example of the lymphoma is anaplastic large cell lymphoma (ALCL). The utility of the Jak3 inhibitors of the present invention for treating ALCL have been demonstrated by the studies presented by Lai, R. *et al.* Jak3 activation is significantly associated with ALK expression in anaplastic large cell lymphoma. *Human Pathology* (2005) **36**, 939-944 and Harrington *et al.* VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth *in vivo*. *Nature Medicinc*e (2004) **3**, 262-267 which are both incorporated in there entirety herein by reference.

[0076] An example of the leukemia is chronic myelogenous leukemia (CML). The utility of the Jak3 inhibitors of the present invention for treating CML have been demonstrated by the studies presented by Harrington *et al.* referenced above. The

aforementioned study further has demonstrated the treatement of acute myelogenous leukemia (AML) via *in vivo* experiments.

[0077] The comounds of the present invention are also useful in treating non-hemotological malignancies, including pancreatic and colon cancer. [See Harrington *et al.*, *op. cit.* for *in vivo* tests.]

[0078] The Jak3 inhibitors of the present invention are additionally useful in treating cardiovascular disease.

[0079] The following examples will further describe the invention, and are used for the purposes of illustration only, and should not be considered as limiting the invention being disclosed.

EXAMPLES

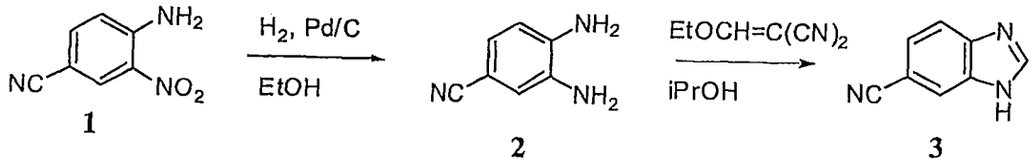
[0080] The following abbreviations and terms have the indicated meaning throughout:

Ac =	acetyl
Bu =	butyl
DCM =	dichloromethane = methylene chloride = CH_2Cl_2
DEAD =	diethyl azodicarboxylate
DIC =	diisopropylcarbodiimide
DIEA =	N,N-diisopropylethyl amine
DMF =	N,N-dimethylformamide
DMSO =	dimethyl sulfoxide
EA (EtOAc)=	Ethyl Acetate
GC =	gas chromatography
h=	hours
HOAc =	acetic acid
HOBt =	hydroxybenzotriazole
Me =	methyl
$Pd(dppf)_2Cl_2$ =	dichloro[1,1'-bis(diphenylphosphinoferrocene]palladium
Ph =	phenyl
PhOH =	phenol
RT =	room temperature
sat'd =	saturated
s- =	secondary
t- =	tertiary
TBDMS =	t-butyldimethylsilyl
TFA =	trifluoroacetic acid
THF =	tetrahydrofuran
TMOF =	trimethyl orthoformate

TMS = trimethylsilyl
tosyl = p-toluenesulfonyl
Trt = triphenylmethyl

Examples 1-15 describe syntheses of certain precursors and intermediates of the invention.

[0081] Example 1. Synthesis of 3,4-Diaminobenzonitrile



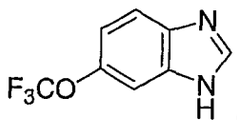
1 2 3

[0082] A solution of 4-amino-3-nitrobenzonitrile (**1**) (3.0 g) in ethanol (80 mL) was sparged for 5 minutes with nitrogen. Palladium on carbon (10%, 300 mg) was added and the mixture was saturated with hydrogen. The mixture was stirred under a hydrogen balloon for seven hours. The mixture was sparged with nitrogen and filtered through celite. The filtrate was concentrated *in vacuo* to provide the title compound, 3,4-diaminobenzonitrile (**2**).

[0083] Example 2: Synthesis of 3H-Benzo[d]imidazole-5-carbonitrile

[0084] A mixture of 3,4-diaminobenzonitrile (**2**) (1.0 g) and (ethoxymethylene)malononitrile (1.4 g) was refluxed in 50 mL of isopropyl alcohol for 16 h. The mixture was concentrated *in vacuo* to provide the title compound, 3H-benzo[d]imidazole-5-carbonitrile (**3**).

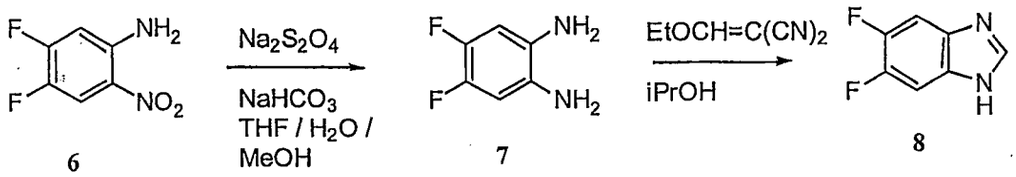
[0085] Example 3: Synthesis of 6-(Trifluoromethoxy)-1H-benzo[d]imidazole



4

[0086] 6-(trifluoromethoxy)-1H-benzo[d]imidazole (**4**) was prepared in two steps from 2-nitro-4-(trifluoromethoxy)aniline (**5**) using procedures identical to those used to make 3H-benzo[d]imidazole-5-carbonitrile (**3**) from 4-amino-3-nitrobenzonitrile (**1**, examples 1, 2).

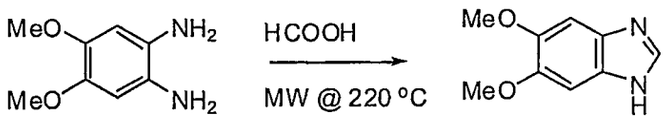
[0087] Example 4: Synthesis of 5,6-Difluoro-1H-benzo[d]imidazole



6 7 8

[0088] A solution of 4,5-difluoro-2-nitroaniline (**6**)(1.0 g) in 30 mL of THF was treated with a solution comprised of 6 g of $Na_2S_2O_4$ and 3 g $NaHCO_3$ in 30 mL of water. Methanol (10 mL) was added after the addition of the aqueous solution so that the mixture remained homogeneous. The mixture was stirred for two hours and then diluted with 100 mL of ethyl acetate and 100 mL of water. The organic layer was separated and the aqueous layer was extracted again with 100 mL of methylene chloride. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to provide the crude intermediate 4,5-difluorobenzene-1,2-diamine (**7**). The intermediate was refluxed with (ethoxymethylene)malononitrile (1.1 g) in 25 mL of isopropyl alcohol for 16 h. The mixture was concentrated *in vacuo* and the resulting crude product was suspended in water and filtered. The precipitate was washed with water and air-dried to provide 380 mg of 5,6-difluoro-1H-benzo[d]imidazole (**8**).

[0089] Example 5: Synthesis of 5,6-Dimethoxy-1H-benzo[d]imidazole

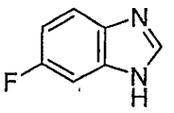


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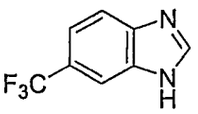
[0090] The title compound 5,6-dimethoxy-1H-benzo[d]imidazole (**10**) was made by heating 4,5-dimethoxy-1,2-phenylenediamine dihydrochloride (**9**) in formic acid at 220 °C in a microwave followed by concentration *in vacuo*.

[0091] Example 6: Synthesis of 6-Fluoro-1H-benzo[d]imidazole (11) and 6-(trifluoromethyl)-1H-benzo[d]imidazole (12).

[0092] The title compounds were by made as described in US Application Publication No. 2004/0087601, of some of the present inventors.



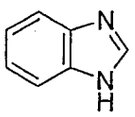
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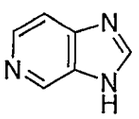
12

[0093] Example 7: Benzimidazole (13), 5-azabenzimidazole (14), 6-chloro-5-fluorobenzimidazole (15), and 5-methylbenzimidazole (16).

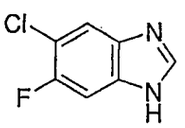
[0094] The title compounds were commercially available.



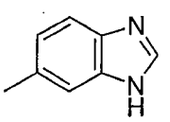
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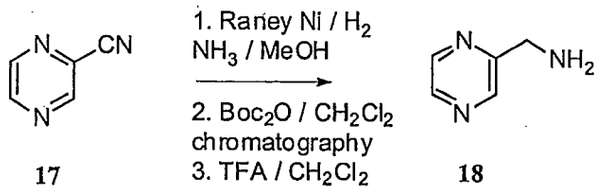


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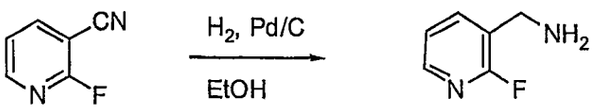
[0095] Example 8. Synthesis of the primary amine, pyrazin-2-ylmethanamine



17 18

[0096] Raney nickel catalyst was carefully washed with THF and methanol making sure that the catalyst remained moist. The weight of the moist catalyst was 2.5 g after washing. This material was added to a solution of pyrazinecarbonitrile (**17**) (3.0 g) in 7N methanolic ammonia (120 mL). The mixture was shaken under a 50 p.s.i. atmosphere of hydrogen for 1.5 hours. The mixture was filtered and the filtrate was concentrated *in vacuo* to provide the crude title compound. Purification was accomplished by conversion of the crude amine to the tert-butyl carbamate with excess di-*tert*-butyl dicarbonate in methylene chloride. Column chromatography (70:27:3 hexanes:ethyl acetate:methanol) provided 0.50 g of pure tert-butyl pyrazin-2-ylmethylcarbamate. Pure pyrazin-2-ylmethanamine (**18**) was obtained as the TFA salt from deprotection of the carbamate with 1:1 TFA / CH_2Cl_2.

[0097] Example 9: Synthesis of 3-Aminomethyl-2-fluoropyridine

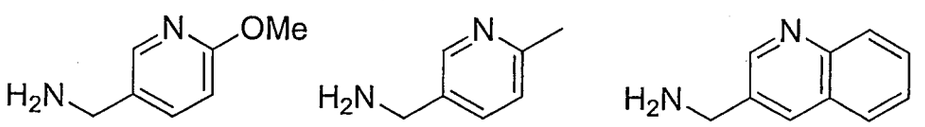


19 20

[0098] A round bottom flask was charged with 0.3g (2.46mM) of 3-cyano-2-fluoropyridine (**19**), which was then diluted in 20mL EtOH. The solution was flushed with argon, and then while under a blanket of argon, 60mg of 10% Pd/C (20% by weight), was added. The system was then sealed by septum and put under vacuum. A hydrogen balloon was then added, and the reaction was stirred for three hours (followed by TLC). The reaction was then put under vacuum again, then exposed to air, and filtered (keeping catalyst wet). The resulting solution was dried and evaporated to give 0.28g (90%) of the title compound, 3-aminomethyl-2-fluoropyridine (**20**).

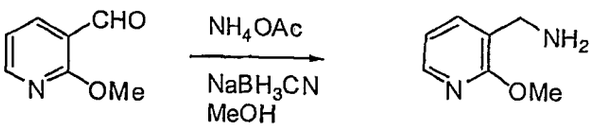
[0099] Example 10: Synthesis of 3-Aminomethyl-6-methoxypyridine (21), 3-Aminomethyl-6-methylpyridine (22), and 3-Aminomethylquinoline (23).

[00100] The title amines were obtained from the corresponding nitriles using the same procedure that was used to obtain 3-aminomethyl-2-fluoropyridine (**20**) from 3-cyano-2-fluoropyridine (see Example 9).



21 22 23

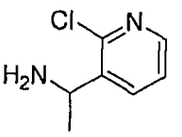
[00101] Example 11: Synthesis of 3-aminomethyl-2-methoxypyridine



24 25

[00102] A round bottom flask was charged with 0.44g (3.23mM) of 2-methoxy-3-pyridine carboxaldehyde (**24**), 1.24g (16.15mM) of ammonium acetate, and 0.61g (19.69mM) of sodium cyanoborohydride. The flask was then flushed with argon, and then 50mL of dry MeOH was added by syringe. The reaction was stirred for 2 days, at which point the MeOH was evaporated off. 25mL of water was added, and the mixture was brought to pH 2 with conc. HCl. This was extracted twice with EtOAc to remove the alcohol side product. The mixture was brought to pH 10 using sodium hydroxide pellets, saturated with NaCl, and extracted twice with DCM and once with EtOAc. The combined organics were dried and evaporated to give 0.31g (69%) of 3-aminomethyl-2-methoxypyridine (**25**).

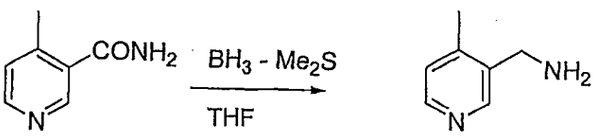
[00103] Example 12: Synthesis of 3-(α-aminoethyl)-2-chloropyridine (26)



26

[00104] The title amine was obtained from the corresponding ketone using the same procedure that was used to obtain 3-aminomethyl-2-methoxypyridine from 2-methoxy-3-pyridine carboxaldehyde (**24; Example 11**).

[00105] Example 13: Synthesis of 3-aminomethyl-4-methylpyridine

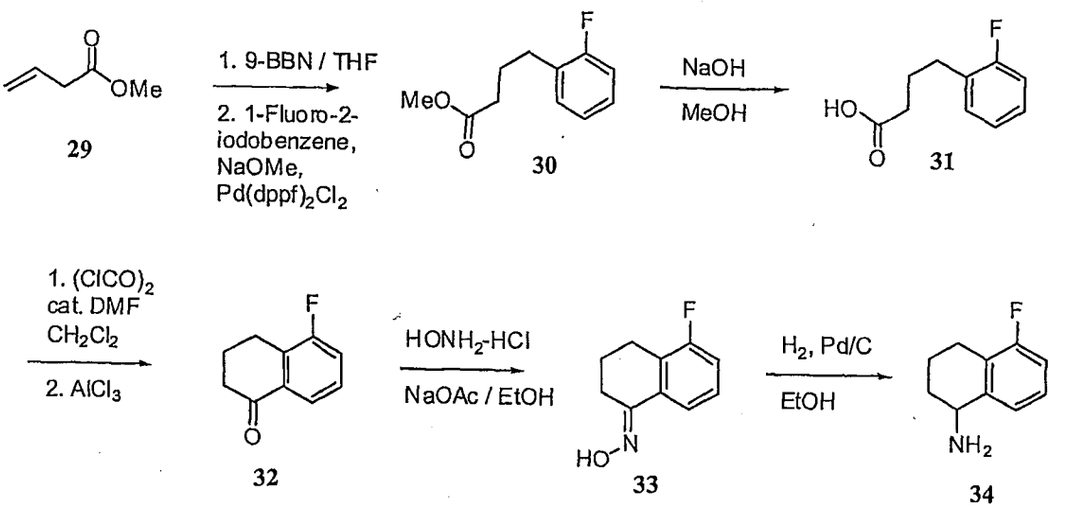


27 **28**

40

[00106] A round bottom flask was charged with 0.45g (3.30mM) of 4-methylnicotinamide (**27**). The flask was flushed with argon, and 50mL of dry THF was added by syringe. The resulting solution was cooled to 0 dg C, and 2.5mL (4.96mM) of a 2M solution of borane-dimethylsulfide complex (in THF) was added. A bubbler was attached, and the solution was allowed to warm to RT overnight. The solution was quenched with MeOH, and dried and evaporated to give 0.38g (95%) of 3-aminomethyl-4-methylpyridine (**28**).

[00107] Example 14: Synthesis of 5-fluoro-1,2,3,4-tetrahydronaphthalen-1-amine



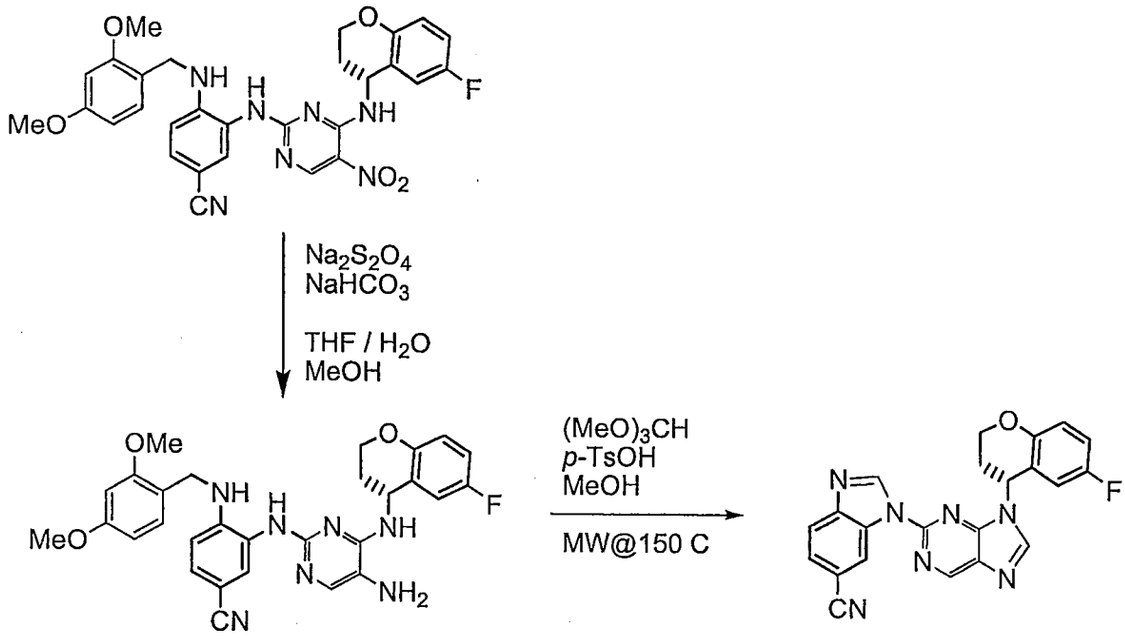
[00108] **Methyl 4-(2-fluorophenyl)butanoate** (2-(4-methylbutanoate)fluorobenzene, **30**). A round bottom flask was sealed with a rubber septum, flushed with argon, then charged with 5.32mL of methyl 3-buteneoate (**29**) and 100mL of a 0.5M solution of 9-BBN in THF. The solution was stirred at RT for three hours. A 2-necked round bottom flask was equipped with a condenser and flushed with argon, then charged with 7.36g of sodium methoxide and 1.11g of $Pd(dppf)_2Cl_2$. To this mixture were added 20mL of dry THF and 5.22mL of 1-fluoro-2-iodobenzene. The hydroboration solution was added via canula and the resulting mixture was refluxed for 16 hours. The solution was cooled to RT, diluted with 150mL of water, and extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. Column chromatography (5% EtOAc/hexanes) gave 1.79 g methyl 4-(2-fluorophenyl)butanoate (**30**).

[00109] **4-(2-Fluorophenyl)butanoic acid (31).** A round bottom flask was charged with 1.79g of 2-(4-methylbutanoate)fluorobenzene, which was dissolved in 17mL of MeOH. To this solution was added a solution of 1 g of sodium hydroxide. The resulting mixture was stirred 20 hours at RT. The solvent was evaporated and the crude material diluted with 15mL of 0.5M HCl. Extraction with DCM three times gave 1.17g (92%) of 4-(2-fluorophenyl)butanoic acid (**31**).

[00110] **5-Fluoro-3,4-dihydronaphthalen-1(2H)-one** (**32**). A round bottom flask was charged with 0.15 g of 4-(2-fluorophenyl)butanoic acid, which was dissolved in 20mL DCM and cooled to 0 °C. Oxalyl chloride (0.15mL) was added, followed by 1 drop of DMF. A drying tube was attached, and the solution was stirred at 0 °C for two hours. Aluminum chloride (0.121g) was added and the solution was allowed to slowly warm to RT overnight. The mixture was poured onto ice water, and extracted three times with DCM. The combined organic layers were washed with 0.5 M NaOH and brine. The organic phase was dried, evaporated, and purified by column chromatography (eluting with 20% EtOAc/Hexanes), to give 0.07g (53%) of 5-fluoro-3,4-dihydronaphthalen-1(2H)-one (**32**).

[00111] **5-Fluoro-1,2,3,4-tetrahydronaphthalen-1-amine (34).** A round bottom flask was charged with 0.5g of 5-fluoro-3,4-dihydronaphthalen-1(2H)-one, 0.28g of hydroxylamine hydrochloride, and 0.34g of sodium acetate. A condenser was attached, and the flask was purged with argon. 20mL of dry EtOH was added, and the mixture was stirred at reflux for 18 hours. The solution was cooled to RT, diluted with EtOAc, and washed with water. The organic phase was dried with sodium sulfate and evaporated to give 0.5g of the intermediate 5-fluoro-3,4-dihydronaphthalen-1(2H)-one oxime (**33**), which was reduced with Pd/C in EtOH with hydrogen (50psi), to give 0.43g (86%) of 5-fluoro-1,2,3,4-tetrahydronaphthalen-1-amine (**34**).

[00112] Example 15: Synthesis of 3-(9-((*R*)-6-fluorochroman-4-yl)-9*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile

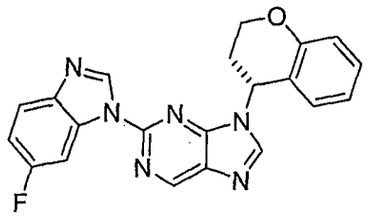


[00113] To a solution of (*R*)-4-(2,4-dimethoxybenzylamino)-3-(4-(6-fluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)benzonitrile (prepared as described below in example 26, paragraph [0157]) (12 mg) in THF (5 mL) was added a premixed solution of sodium hydrosulfite (100 mg) and sodium bicarbonate (50 mg) in water (10 mL). MeOH (1 mL) was also added to aid solution of the mixture, which was stirred at room temperature for 30 min, when sodium chloride was added to saturate the solution. The resultant mixture was extracted with EtOAc (2x), the combined organics were dried, filtered and evaporated to yield (*R*)-4-(2,4-dimethoxybenzylamino)-3-(5-amino-4-(6-fluorochroman-4-ylamino)pyrimidin-2-ylamino)benzonitrile that was used as such for the next step, $MH^+ = 542$.

[00114] To a microwave vial was added the above amine, a catalytic amount of *para*-toluene sulfonic acid monohydrate, trimethyl orthoformate (0.5 mL) and MeOH (1 mL). The vial was capped and heated in an Emrys Optimizer microwave at 150 °C for 5 minutes. The mixture was concentrated *in vacuo*, and purified by RP HPLC to yield 4.6 mg of the titled product as the TFA salt, NMR $CDCl_3$ ^1H δ 9.5 (br s, 1H), 9.3 (s, 1H), 9.0

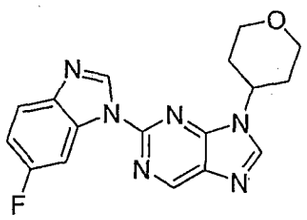
(s, 1H), 8.2 (br s, 1H), 8.0 (d, 1H), 7.7 (d, 1H), 7.1-7.0 (m, 2H), 6.6 (dd, 1H), 6.0 (t, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 2.7 (m, 2H); ^{19}F δ -121, -76 ppm; $MH^+ = 412$.

[00115] Synthesis of 9-((*R*)-Chroman-4-yl)-2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9*H*-purine.



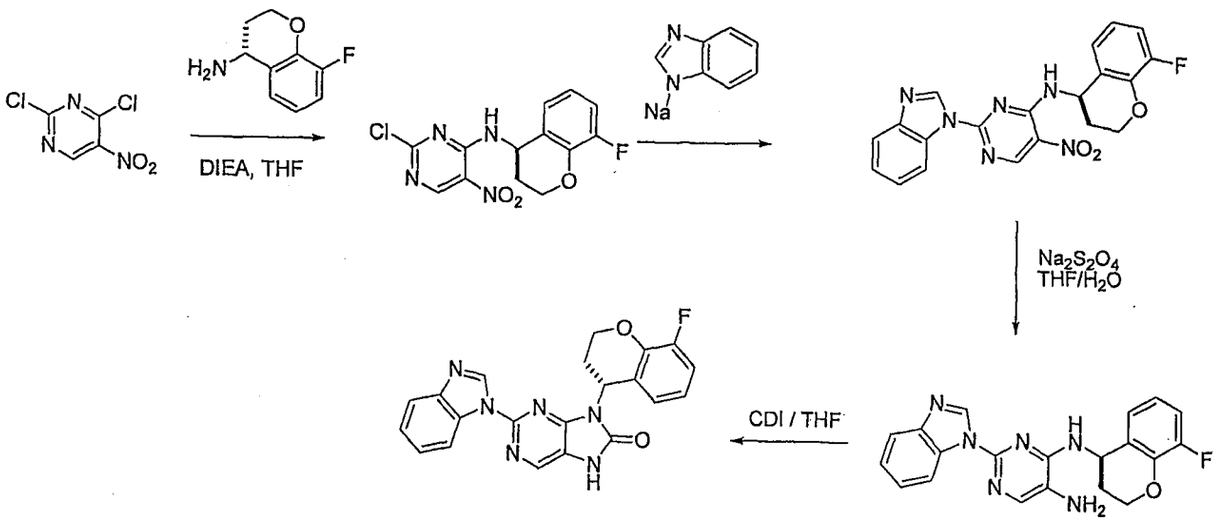
[00116] The title compound as a TFA salt was synthesized from (*R*)-tert-butyl 2-(4-(chroman-4-ylamino)-5-nitropyrimidin-2-ylamino)-4-fluorophenylcarbamate via the procedure described in Example 15. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (s, 2H), 8.27 (dd, 1H), 7.89 (s, 1H), 7.78 (dd, 1H), 7.32 (td, 1H), 7.32 (td, 1H), 7.13 (td, 1H), 7.1-6.9 (m, 3H), 6.00 (t, 1H), 4.4-4.3 (m, 2H), 4.2-4.1 (m, 2H), 2.7-2.5 (m, 2H). ^{19}F NMR: δ -116.4.

[00117] Synthesis of 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-(tetrahydro-2*H*-pyran-4-yl)-9*H*-purine.



[00118] The title compound as a TFA salt was synthesized from tert-butyl 4-fluoro-2-(5-nitro-4-(tetrahydro-2H-pyran-4-ylamino)pyrimidin-2-ylamino)phenylcarbamate via the procedure described in Example 15. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (s, 1H), 9.29 (s, 1H), 8.5-8.6 (m, 1H), 8.40 (s, 1H), 7.9-8.1 (m, 1H), 7.3-7.4 (m, 1H), 4.8-5.0 (m, 1H), 4.2-4.4 (m, 2H), 3.7-3.8 (m, 2H), 3.05 (d, 1H), 2.2-2.4 (m, 3H). ^{19}F NMR: δ -112.4.

[00119] Example 16: Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one

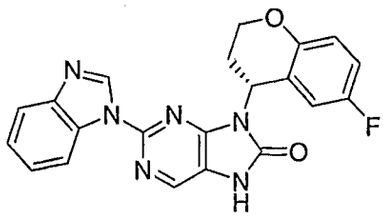


[00120] **2-(1*H*-Benzo[d]imidazol-1-yl)-*N*-((*R*)-8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine.** (*R*)-8-fluorochroman-4-amine (60 mg, Example 29) was added to a solution of 2,4-dichloro-5-nitropyrimidine (70 mg) and DIEA (0.14 mL) in THF (5 mL) at -78 °C. The reaction mixture was stirred for a further 15 min at -78 °C then removed from the cold bath and allowed to warm to RT. A one molar solution of the sodium salt of benzimidazole (0.7 ml, stock solution prepared via the addition of sodium hydride to a benzimidazole solution in THF) was added to the reaction intermediate ((*R*)-2-chloro-*N*-(8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine) and the resulting mixture was stirred at RT overnight. Purification via column chromatography (elution with 1 MeOH/DCM) gave the titled compound (120 mg), $MH^+ = 407$.

[00121] **2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one.** A freshly prepared solution of sodium hydrosulfite (tech, 0.5 g) and sodium bicarbonate (0.25 g) in H_2O (5 mL) was added to a solution of the above nitro compound (120 mg) in THF (10 mL). The mixture was stirred vigorously for 30 min then extracted with EtOAc (2 x) and DCM (2 x), the combined organics were washed with brine, dried, filtered and concentrated to yield the intermediate 2-(1*H*-benzo[*d*]imidazol-1-yl)-N^4-((*R*)-8-fluorochroman-4-yl)pyrimidine-4,5-diamine that was used as such in the next step.

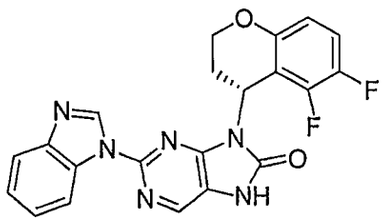
[00122] Carbonyldiimidazole (0.2 g) was added to a solution of the above amine in THF (10 mL). The resulting mixture was stirred at RT overnight, silica gel was added, then the solvents were removed under reduced pressure and purified via column chromatography, elution with 5 % MeOH/DCM, to yield the titled product (28 mg), MH^+ = 403, ^1H NMR ($CDCl_3$) δ 10.6 (s, 1H), 8.9 (s, 1H), 8.3 (s, 1H), 7.8 (m, 2H), 7.3 (m, 2H), 7.0 (m, 1H), 6.7 (m, 1H), 5.9 (dd, 1H), 4.7 (m, 1H), 4.4 (t, 1H), 2.7 (m, 1H), 2.3 (m, 1H) ppm, ^{19}F NMR δ -135.7 (m). Chiral HPLC – no evidence of other enantiomer, Method; Chiralcel OD-H (0.46 x 25 cm analytical column, Daicel Chemical Industries) isocratic 15 % (0.05% TFA/EtOH) 85 % (0.05 % TFA/Hex), Rt = 19.5 min (*R*)-enantiomer, Rt = 22.4 min (*S*)-enantiomer.

[00123] Synthesis of 2-(1H-benzo[d]imidazol-1-yl)-9-((R)-6-fluorochroman-4-yl)-7H-purin-8(9H)-one.



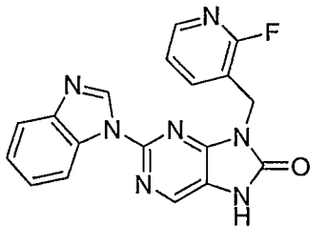
[00124] The title compound was synthesized from (R)-6-fluorochroman-4-amine using the procedures outline in Example 16. ^1H NMR (300 MHz, $CDCl_3$): δ 10.28 (s, 1H), 8.82 (s, 1H), 8.28 (s, 1H), 7.94 (d, 1H), 7.79 (d, 1H), 7.2-7.4 (m, 2H), 6.8-7.1 (m, 2H), 6.66 (dd, 1H), 5.92 (br t, 1H), 4.55 (m, 1H), 4.33 (m, 1H), 2.90 (m, 1H), 2.31 (m, 1H).

[00125] Synthesis of 2-(1H-benzo[d]imidazol-1-yl)-9-((R)-5,6-difluorochroman-4-yl)-7H-purin-8(9H)-one.



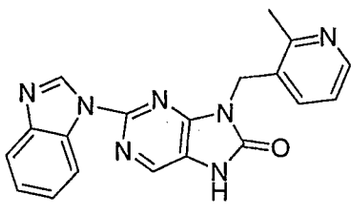
[00126] The title compound was synthesized from (R)-5,6-difluorochroman-4-amine (obtained by resolution of (+/-)-5,6-difluorochroman-4-amine using the resolution procedure outlined in Example 29) using the procedures outline in Example 16. ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.62 (s, 1H), 8.18 (s, 1H), 8.0-8.1 (m, 1H), 7.6-7.7 (m, 1H), 7.2-7.3 (m, 1H), 6.9-7.1 (m, 2H), 6.7-6.8 (m, 1H), 5.86 (br t, 1H), 4.4-4.5 (m, 1H), 4.2-4.3 (m, 1H), 2.5-2.6 (m, 1H), 2.3-2.4 (m, 1H).

[00127] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((2-fluoropyridin-3-yl)methyl)-7H-purin-8(9*H*)-one.



[00128] The title compound was synthesized from 3-aminomethyl-2-fluoropyridine via the procedure described in Example 16. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 9.0 (d, 1H), 8.4 (m, 1H), 8.2 (d, 1H), 7.8 (m, 2H), 7.4 (m, 3H), 7.2 (t, 1H), 4.3 (s, 2H), ppm.

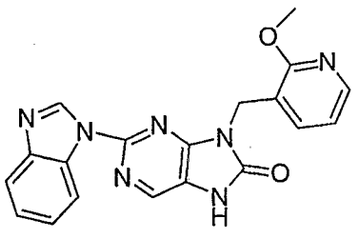
[00129] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((2-methylpyridin-3-yl)methyl)-7*H*-purin-8(9*H*)-one.



[00130] The title compound was synthesized from 3-aminomethyl-2-methylpyridine via the procedure described in Example 16. ^{1}H-NMR ($CDCl_3$) δ 9.4 (s, 1H), 8.6 (d, 1H), 8.5 (d, 1H), 8.4 (d, 1H), 8.2 (s, 1H), 7.7 (d, 1H), 7.6 (t, 1H), 7.4 (m, 2H), 5.2 (s, 2H), 2.9 (s, 3H), ppm.

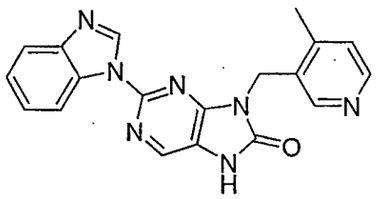
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[00131] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((2-methoxypyridin-3-yl)methyl)-7*H*-purin-8(9*H*)-one.



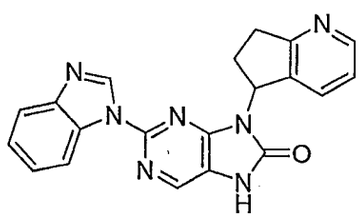
[00132] The title compound was synthesized from 3-aminomethyl-2-methoxypyridine via the procedure described in Example 16. ^{1}H-NMR ($CDCl_3$) δ 9.1 (s, 1H), 8.6 (d, 1H), 8.2 (s, 1H), 8.0 (d, 1H), 7.7 (s, 1H), 7.7 (d, 1H), 7.5 (d, 1H), 7.3 (m, 2H), 6.80 (t, 1H), 5.1 (s, 2H), 3.9 (s, 3H), ppm.

[00133] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((4-methylpyridin-3-yl)methyl)-7*H*-purin-8(9*H*)-one.



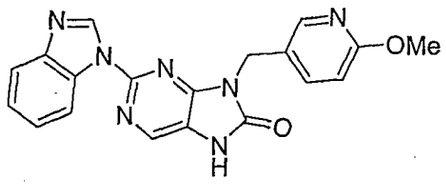
[00134] The title compound was synthesized from 3-aminomethyl-4-methylpyridine via the procedure described in Example 16. ^{1}H-NMR ($CDCl_3$) δ 8.9 (s, 1H), 8.5 (s, 1H), 8.3 (m, 1H), 8.2 (m, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.3 (m, 1H), 7.0 (m, 2H), 5.2 (s, 2H), 2.5 (s, 3H), ppm.

[00135] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(6,7-dihydro-5H-cyclopenta[*b*]pyridin-5-yl)-7*H*-purin-8(9*H*)-one.



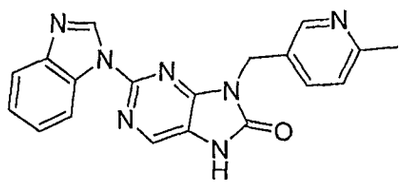
[00136] The title compound was synthesized from 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-5-amine (WO 2003/045924) via the procedure described in Example 16. ^{1}H-NMR ($CDCl_3$) δ 8.8 (s, 1H), 8.6 (d, 1H), 8.3 (s, 1H), 7.8 (dd, 1H), 7.6 (dd, 1H), 7.4 (d, 1H), 7.3-7.1 (m, 3H), 6.3 (t, 1H), 3.6-3.5 (m, 1H), 3.4-3.2 (m, 1H), 2.9-2.6 (m, 2H) ppm.

[00137] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((6-methoxypyridin-3-yl)methyl)-7*H*-purin-8(9*H*)-one.



[00138] The title compound was synthesized from 3-aminomethyl-6-methoxypyridine via the procedure described in Example 16. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.5 (d, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.8 (m, 2H), 7.4 (t, 2H), 6.7 (d, 1H), 5.1 (s, 2H), 3.8 (s, 3H) ppm.

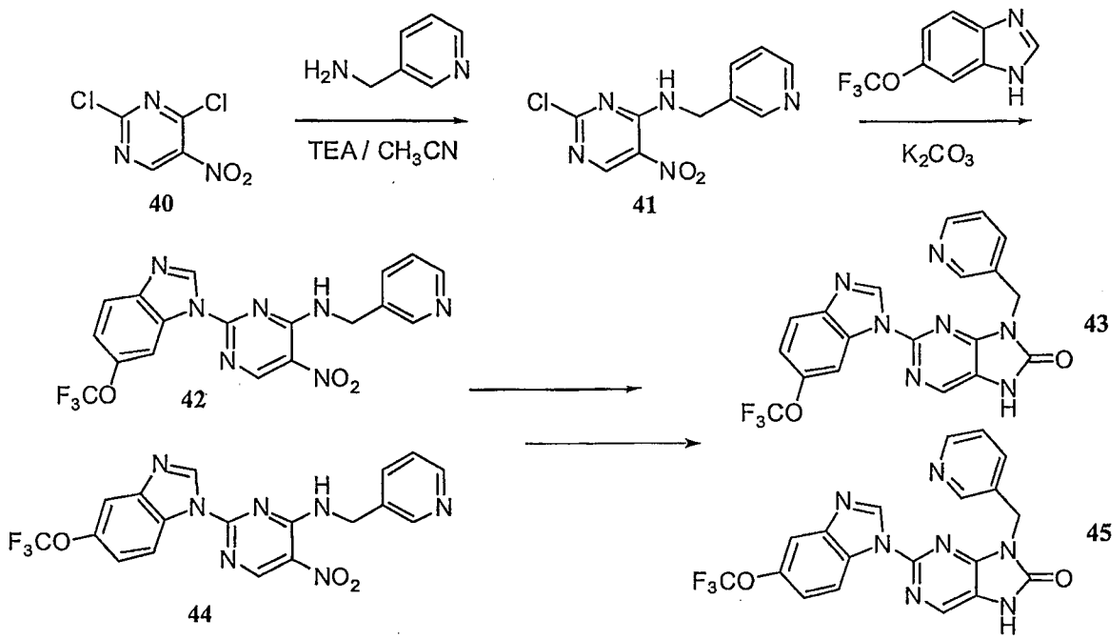
[00139] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-((6-methylpyridin-3-yl)methyl)-7*H*-purin-8(9*H*)-one.



[00140] The title compound was synthesized from 3-aminomethyl-6-methylpyridine via the procedure described in Example 16. ^{1}H-NMR ($CDCl_3$) δ 9.5 (s, 1H), 9.2 (s, 1H), 8.9 (s, 1H), 8.7 (d, 1H), 8.4 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 7.5 (m, 2H), 5.5 (s, 2H), 2.6 (s, 3H) ppm.

[00141] Example 17: Non-regiospecific synthesis of benzimidazole purinone derivatives: Synthesis of 5-Nitro-N-(pyridin-3-ylmethyl)-2-(6-(trifluoromethoxy)-1H-

benzo[d]imidazol-1-yl)pyrimidin-4-amine (**42**) AND 5-nitro-N-(pyridin-3-ylmethyl)-2-(5-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)pyrimidin-4-amine (**44**).



[00142] 2-Chloro-5-nitro-N-(pyridin-3-ylmethyl)pyrimidin-4-amine (41). A solution of 2,4-dichloro-5-nitropyrimidine (**40**) (5 g) in methylene chloride (60 mL) was cooled to -78 °C and treated with 3-(aminomethyl)pyridine (2.8 g). The mixture was stirred at -78 °C for six hours, and concentrated *in vacuo* at RT to provide crude 2-chloro-5-nitro-N-(pyridin-3-ylmethyl)pyrimidin-4-amine (**41**), which was used without further purification.

[00143] 5-Nitro-N-(pyridin-3-ylmethyl)-2-(6-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)pyrimidin-4-amine (42) and 5-nitro-N-(pyridin-3-ylmethyl)-2-(5-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)pyrimidin-4-amine (44). A suspension of crude 2-chloro-5-nitro-N-(pyridin-3-ylmethyl)pyrimidin-4-amine (52 mg) in acetonitrile (10 mL) was treated with 6-(trifluoromethoxy)-1H-benzo[d]imidazole (40 mg), potassium carbonate (0.5 g), and heated at 80 °C for four hours. The mixture was diluted with water and extracted with methylene chloride. The organic layer was separated, dried with sodium sulfate, filtered, and concentrated *in vacuo*. Column chromatography (70:22:8 methylene

chloride:ethyl acetate:methanol) provided 12 mg of 5-nitro-N-(pyridin-3-ylmethyl)-2-(5-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)pyrimidin-4-amine as the first eluting isomer and 15 mg of 5-nitro-N-(pyridin-3-ylmethyl)-2-(6-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)pyrimidin-4-amine as the second eluting isomer.

[00144] High R_f isomer: ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.9 (s, 1H), 8.8 (m, 1H), 8.6 (s, 1H), 8.5 (d, 1H), 8.2 (d, 1H, assign: H-7 of benzimidazole ring), 7.6 (d, 1H), 7.6 (s, 1H, assign: H-4 of benzimidazole ring), 7.2 (dd, 1H), 4.9 (d, 2H).

[00145] Low R_f isomer: ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.9 (s, 1H), 8.8 (m, 1H), 8.6 (s, 1H), 8.5 (d, 1H), 8.2 (s, 1H, assign: H-7 of benzimidazole ring), 7.7 (d, 1H, assign: H-4 of benzimidazole ring), 7.6 (d, 1H), 7.2 (dd, 1H), 7.1 (d, 1H), 4.9 (d, 2H).

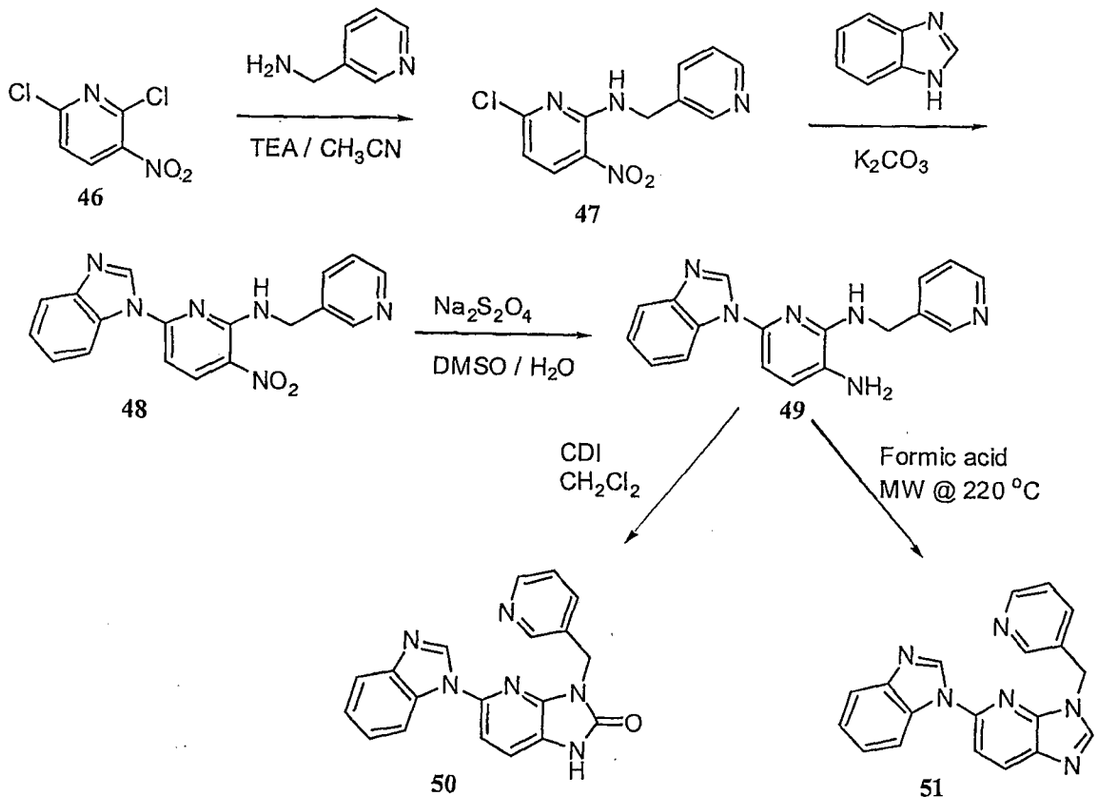
[00146] Example 18: Non-regiospecific synthesis of benzimidazole purinone derivatives: Synthesis of 9-(Pyridin-3-ylmethyl)-2-(6-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)-7H-purin-8(9H)-one (**43**) AND 9-(pyridin-3-ylmethyl)-2-(5-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)-7H-purin-8(9H)-one (**45**).

[00147] The title compounds were synthesized from 5-nitro-N-(pyridin-3-ylmethyl)-2-(6-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)pyrimidin-4-amine (**42**) and 5-nitro-N-(pyridin-3-ylmethyl)-2-(5-(trifluoromethoxy)-1H-benzo[d]imidazol-1-yl)pyrimidin-4-amine (**44**) using the same procedures that were used to convert (R)-tert-butyl 2,4-dimethoxybenzyl(5-nitro-6-(1-(pyridin-3-yl)ethylamino)pyridin-2-yl)carbamate to (R)-tert-butyl 2,4-dimethoxybenzyl(2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)carbamate (**67**; Example 22 below).

[00148] 6-Trifluoromethoxy isomer (non-salt): ^{1}H-NMR (CD_3OD) δ 9.3 (s, 1H), 8.8 (br s, 1H), 8.6 (s, 1H, assign: H-7 of benzimdazole ring), 8.6 (m, 1H), 8.4 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H, assign: H-4 of benzimidazole ring), 7.5 (dd, 1H), 7.4 (dd, 1H), 5.4 (s, 2H).

[00149] 5-Trifluoromethoxy isomer (non-salt): ^{1}H-NMR (CD_3OD) δ 9.3 (s, 1H), 8.8 (s, 1H), 8.7 (d, 1H, assign: H-7 of benzimdazole ring), 8.5 (d, 1H), 8.3 (s, 1H), 7.9 (d, 1H), 7.6 (s, 1H, assign: H-4 of benzimidazole ring), 7.4 (dd, 1H), 7.3 (dd, 1H), 5.3 (s, 2H).

[00150] Example 19: Non-regiospecific synthesis of an oxoimidazopyridine and an imidazopyridine derivative: Synthesis of 5-(1H-Benzo[d]imidazol-1-yl)-3-(pyridin-3-ylmethyl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (**50**) AND 5-(1H-benzo[d]imidazol-1-yl) 3-(pyridin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine (**51**).



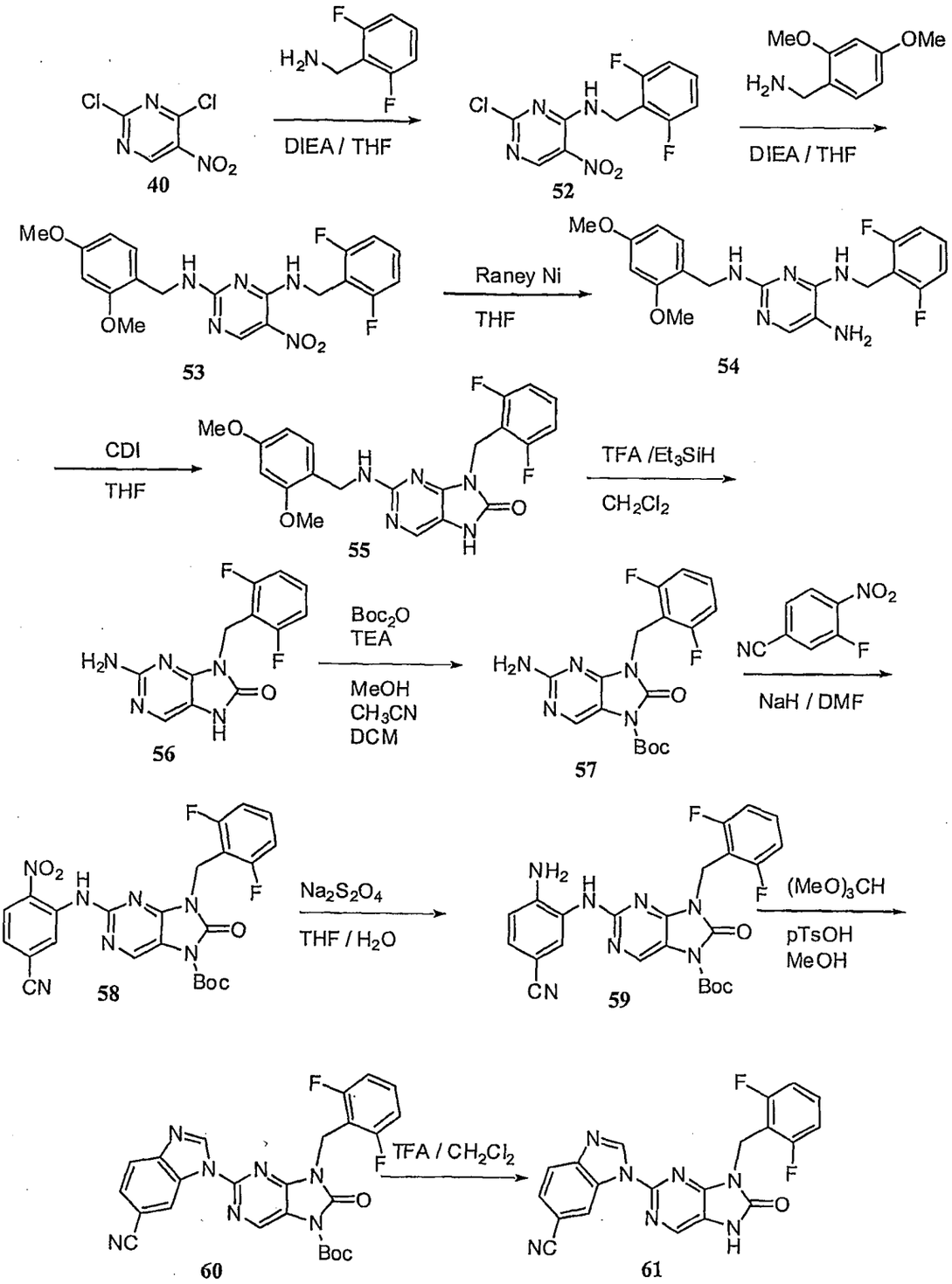
[00151] **6-(1H-Benzo[d]imidazol-1-yl)-3-nitro-N-(pyridin-3-ylmethyl)pyridin-2-amine (48).** A solution of 2,6-dichloro-3-nitropyridine (**46**) (0.5 g) in acetonitrile (20 mL) was cooled to 0 °C and treated with triethylamine (0.36 mL) followed by 3-(aminomethyl)pyridine (0.26 mL). The mixture was stirred for 30 minutes at 0 °C and eight hours at RT. The resulting solution, which contained the intermediate 6-chloro-3-

nitro-N-(pyridin-3-ylmethyl)pyridin-2-amine (**47**), was transferred to a sealed tube containing benzimidazole (0.84 g) and potassium carbonate (3 g) and heated at 70 °C for 16 h. The mixture was cooled and filtered. The precipitated was washed with water and air-dried to provide 239 mg of the title compound (**48**).

[00152] 5-(1H-Benzo[d]imidazol-1-yl)-3-(pyridin-3-ylmethyl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (**50**) and 5-(1H-benzo[d]imidazol-1-yl)-3-(pyridin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine (**51**). A solution of 6-(1H-benzo[d]imidazol-1-yl)-3-nitro-N-(pyridin-3-ylmethyl)pyridin-2-amine (48) (50 mg) in 1 mL of DMSO was treated with a solution of $Na_2S_2O_4$ (300 mg) in 1 mL of water. The mixture was stirred for two hours and diluted with 50 mL of ethyl acetate. The mixture was washed three times with 50 mL aliquots of saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the intermediate 6-(1H-benzo[d]imidazol-1-yl)-N2-(pyridin-3-ylmethyl)pyridine-2,3-diamine (49). Half of the intermediate was dissolved in methylene chloride (2 mL) and treated with 1,1'-carbonyldiimidazole (46 mg) at RT for 16 h. The resulting crude mixture was purified by preparative TLC (1000 microns, 5% MeOH / CH_2Cl_2) to provide 7.1 mg of 5-(1H-benzo[d]imidazol-1-yl)-3-(pyridin-3-ylmethyl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (50): ^{1}H-NMR ($CDCl_3$) δ 10.0 (br s, 1H), 8.9 (s, 1H), 8.6 (d, 1H), 8.5 (s, 1H), 7.9 (m, 2H), 7.8 (m, 1H), 7.6 (d, 1H), 7.4 (m, 2H), 7.4 (m, 1H), 7.3 (d, 1H), 5.2 (s, 2H). The other half of the reduced intermediate was dissolved in 1 mL of formic acid and heated in a microwave at 220 °C for 10 minutes. The mixture was concentrated *in vacuo*, diluted with methylene chloride, and washed with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried with sodium sulfate, filtered, and concentrated *in vacuo*.

[00153] Purification by preparative TLC (1000 microns, 5% MeOH / CH_2Cl_2) provided 3.5 mg of 5-(1H-benzo[d]imidazol-1-yl)-3-(pyridin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine (**51**): ^{1}H-NMR ($CDCl_3$) δ 8.8 (s, 1H), 8.6 (d, 1H), 8.6 (s, 1H), 8.3 (d, 1H), 8.2 (s, 1H), 8.0 (m, 1H), 7.9 (m, 1H), 7.7 (dd, 1H), 7.6 (d, 1H), 7.4 (m, 2H), 7.3 (m, 1H).

[00154] Example 20: Regiospecific synthesis: Synthesis of 3-(9-(2,6-Difluorobenzyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile



40 52 53 54 55 56 57 58 59 60 61

[00155] ***N*^{2}-(2,4-Dimethoxybenzyl)-*N*^{4}-(2,6-difluorobenzyl)-5-nitropyrimidine-2,4-diamine (53).** 2,6-Difluorobenzylamine (0.24 mL) was added dropwise over one min. to

a solution of 2,4-dichloro-5-nitropyrimidine(**40**) (0.388 g) and DIEA (0.77 mL) in THF in a cold bath set to -78°C. The reaction mixture was stirred for a further 15 min at -78°C then removed from the cold bath and allowed to warm to RT. Additional DIEA (0.77 mL) was added to the reaction intermediate (*N*-(2,6-difluorobenzyl)-2-chloro-5-nitropyrimidin-4-amine) (**52**) followed by the addition of 2,4-dimethoxybenzylamine (0.30 mL) and the resulting mixture was stirred at RT overnight. Purification via column chromatography (eluted with 1 and 2.5 % MeOH/DCM) gave N^2-(2,4-dimethoxybenzyl)-N^4-(2,6-difluorobenzyl)-5-nitropyrimidine-2,4-diamine (**53**) (0.80 g), $MH^+ = 432$.

[00156] **2-(2,4-Dimethoxybenzylamino)-9-(2,6-difluorobenzyl)-7*H*-purin-8(9*H*)-one (55).** Raney Ni was added to a solution of N^2-(2,4-dimethoxybenzyl)-N^4-(2,6-difluorobenzyl)-5-nitropyrimidine-2,4-diamine (0.80 g) in THF (50 mL) under argon flush. The suspension was evacuated, charged with hydrogen (balloon) and stirred for 16 hr. The resulting mixture was filtered through a celite plug that was thoroughly rinsed with THF and MeOH to yield N^2-(2,4-dimethoxybenzyl)-N^4-(2,6-difluorobenzyl)pyrimidine-2,4,5-triamine (**54**) that was used as such in the next reaction.

[00157] Carbonyldiimidazole (0.93 g) was added to a solution of N^2-(2,4-dimethoxybenzyl)-N^4-(2,6-difluorobenzyl)pyrimidine-2,4,5-triamine (**54**) in THF (20 mL) and the resultant mixture stirred at RT overnight, then the solvents were removed under reduced pressure and the taken up in EtOAc and washed trice with water. The organics were dried, filtered and evaporated and purified via column chromatography, elution with 2.5 and 4 % MeOH/DCM, to yield 2-(2,4-Dimethoxybenzylamino)-9-(2,6-difluorobenzyl)-7*H*-purin-8(9*H*)-one (**55**) (0.58 g), $MH^+ = 428$.

[00158] ***tert*-Butyl 9-(2,6-difluorobenzyl)-2-amino-8-oxo-8,9-dihydropurine-7-carboxylate (57).** A 1:1 solution of TFA/DCM (10 mL) was added to 2-(2,4-dimethoxybenzylamino)-9-(2,6-difluorobenzyl)-7*H*-purin-8(9*H*)-one (**55**) (0.58 g) and stirred for 30 min, after which triethylsilane (2 mL) was added and the mixture was stirred an additional 4 hr. The solvents were removed under *in vacuo*, the residue was taken up in minimal MeOH and triturated with Et_2O, to yield the TFA salt of 9-(2,6-

difluorobenzyl)-2-amino-7*H*-purin-8(9*H*)-one **(56)** (0.55 g), $MH^+ = 278$, as a salmon colored solid.

[00159] 9-(2,6-Difluorobenzyl)-2-amino-7*H*-purin-8(9*H*)-one (0.55 g) was dissolved in a mixture of MeOH/ACN/DCM (40 mL), Et_3N (2 mL) and di-*tert*-butyl dicarbonate (0.61 g) were added and the mixture was stirred at RT overnight. The reaction solvents were removed and the crude material was taken up in DCM and washed with H_2O, evaporated and purified via column chromatography, elution with 2 and 3 % MeOH/DCM gave the titled product **(57)** (0.36 g), $MH^+ = 378$, MH^+-Boc = 278 (major), $(M + Na)^+ = 400$ and $(2M + Na)^+ = 777$ were also observed.

[00160] ***tert*-Butyl 9-(2,6-difluorobenzyl)-2-(5-cyano-2-nitrophenylamino)-8-oxo-8,9-dihydropurine-7-carboxylate (58).** Sodium hydride (88 mg, 95%) was added, under argon flush, to a solution of *tert*-butyl 9-(2,6-difluorobenzyl)-2-amino-8-oxo-8,9-dihydropurine-7-carboxylate **(57)** (191 mg) and 3-fluoro-4-nitrobenzonitrile (415 mg) in DMF (5 mL) at -40 °C. The reaction mixture was allowed to warm to -20 °C over 3 hr then quenched by the addition of sat. aq. NH_4Cl, once at RT the mixture was diluted with EtOAc and separated. The organics were washed with brine (3 x), dried, filtered and evaporated, purified via column chromatography, (eluted with DCM and 1 and 2.5 % MeOH/DCM) to yield *tert*-Butyl 9-(2,6-difluorobenzyl)-2-(5-cyano-2-nitrophenylamino)-8-oxo-8,9-dihydropurine-7-carboxylate **(58)** (288 mg), $MH^+ = 524$.

[00161] ***tert*-Butyl 9-(2,6-difluorobenzyl)-2-(6-cyano-1*H*-benzo[*d*]imidazol-1-yl)-8-oxo-8,9-dihydropurine-7-carboxylate (60).** A freshly prepared solution of sodium hydrosulfite (tech, 1 g) and sodium bicarbonate (0.5 g) in H_2O (10 mL) was added to a solution of the above nitro compound **(58)** (288 mg) in THF (10 mL). The mixture was stirred vigorously for 5 min., extracted with DCM (3 x), the combined organics were washed with brine, dried, filtered and concentrated to yield the intermediate *tert*-butyl 9-(2,6-difluorobenzyl)-2-(2-amino-5-cyanophenylamino)-8-oxo-8,9-dihydropurine-7-carboxylate **(59)** that was used as such in the next step.

[00162] A catalytic amount of *para*-toluene sulfonic acid monohydrate was added to a solution of the above amine intermediate and trimethyl orthoformate (3 mL) in MeOH

56

difluorobenzyl)-2-amino-7*H*-purin-8(9*H*)-one **(56)** (0.55 g), $MH^+ = 278$, as a salmon colored solid.

[00159] 9-(2,6-Difluorobenzyl)-2-amino-7*H*-purin-8(9*H*)-one (0.55 g) was dissolved in a mixture of MeOH/ACN/DCM (40 mL), Et_3N (2 mL) and di-*tert*-butyl dicarbonate (0.61 g) were added and the mixture was stirred at RT overnight. The reaction solvents were removed and the crude material was taken up in DCM and washed with H_2O, evaporated and purified via column chromatography, elution with 2 and 3 % MeOH/DCM gave the titled product **(57)** (0.36 g), $MH^+ = 378$, MH^+-Boc = 278 (major), $(M + Na)^+ = 400$ and $(2M + Na)^+ = 777$ were also observed.

[00160] ***tert*-Butyl 9-(2,6-difluorobenzyl)-2-(5-cyano-2-nitrophenylamino)-8-oxo-8,9-dihydropurine-7-carboxylate (58).** Sodium hydride (88 mg, 95%) was added, under argon flush, to a solution of *tert*-butyl 9-(2,6-difluorobenzyl)-2-amino-8-oxo-8,9-dihydropurine-7-carboxylate **(57)** (191 mg) and 3-fluoro-4-nitrobenzonitrile (415 mg) in DMF (5 mL) at -40 °C. The reaction mixture was allowed to warm to -20 °C over 3 hr then quenched by the addition of sat. aq. NH_4Cl, once at RT the mixture was diluted with EtOAc and separated. The organics were washed with brine (3 x), dried, filtered and evaporated, purified via column chromatography, (eluted with DCM and 1 and 2.5 % MeOH/DCM) to yield *tert*-Butyl 9-(2,6-difluorobenzyl)-2-(5-cyano-2-nitrophenylamino)-8-oxo-8,9-dihydropurine-7-carboxylate **(58)** (288 mg), $MH^+ = 524$.

[00161] ***tert*-Butyl 9-(2,6-difluorobenzyl)-2-(6-cyano-1*H*-benzo[*d*]imidazol-1-yl)-8-oxo-8,9-dihydropurine-7-carboxylate (60).** A freshly prepared solution of sodium hydrosulfite (tech, 1 g) and sodium bicarbonate (0.5 g) in H_2O (10 mL) was added to a solution of the above nitro compound **(58)** (288 mg) in THF (10 mL). The mixture was stirred vigorously for 5 min., extracted with DCM (3 x), the combined organics were washed with brine, dried, filtered and concentrated to yield the intermediate *tert*-butyl 9-(2,6-difluorobenzyl)-2-(2-amino-5-cyanophenylamino)-8-oxo-8,9-dihydropurine-7-carboxylate **(59)** that was used as such in the next step.

[00162] A catalytic amount of *para*-toluene sulfonic acid monohydrate was added to a solution of the above amine intermediate and trimethyl orthoformate (3 mL) in MeOH

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Carlos Eduardo Amaya Fernández

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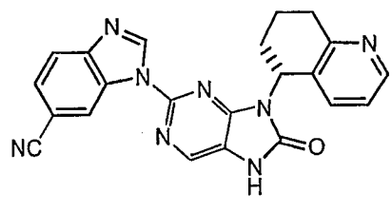
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(10 mL). After 1 hr the crude material was adsorbed onto silica gel and purified by column chromatography (eluted with 1 and 2 % MeOH/DCM) to yield *tert*-Butyl 9-(2,6-difluorobenzyl)-2-(6-cyano-1*H*-benzo[*d*]imidazol-1-yl)-8-oxo-8,9-dihydropurine-7-carboxylate (**60**) (164 mg), MH^+ = 504 and MH^+-BOC = 404.

[00163] 3-(9-(2,6-Difluorobenzyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile (61). A 1:1 solution of TFA/DCM (10 mL) was added to *tert*-Butyl 9-(2,6-difluorobenzyl)-2-(6-cyano-1*H*-benzo[*d*]imidazol-1-yl)-8-oxo-8,9-dihydropurine-7-carboxylate (**60**) and stirred for 1 hr. The solvents were removed *en vacuo* and the resulting solid was triturated with Et_2O, and suspended in 6N HCl. Removal of solvents and trituration with Et_2O of the resulting solid gave the titled compound (**61**) (68 mg) as a HCl salt, MH^+ = 404, ^1H NMR (d_6-DMSO) δ 11.8 (s, 1H), 9.2 (s, 1H), 8.8 (s, 1H), 8.0 (s, 1H), 7.9 (d, 1H), 7.8 (broad s, 1H), 7.4 (d, 1H), 7.4 (quintet, 1H), 7.1 (m, 2H), 5.2 (s, 2H) ppm, ^{19}F NMR δ -114.3 (m).

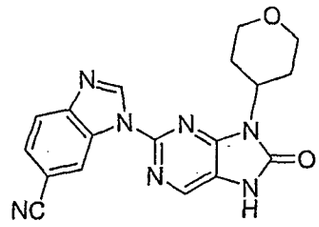
[00164] Synthesis of 3-(8-Oxo-9-((*R*)-5,6,7,8-tetrahydroquinolin-5-yl)-8,9-dihydro-7*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile.



[00165] The title compound was synthesized from (*R*)-5,6,7,8-tetrahydroquinolin-5-amine (obtained via Novozyme 435 resolution (J. Org. Chem., **2003**, *68*, 3546) in a manner similar to that described in Example 29) via the procedure outlined in Example 20. ^1H-NMR (300 MHz, $CDCl_3$+5% CD_3OD) δ 8.9 (br s, 1H), 8.7 (s, 1H), 8.6 (m, 1H), 8.3 (s, 1H), 7.8 (d, 1H), 7.7 (d, 2H), 7.6 (d, 1H), 7.5 (dd, 1H), 5.9 (dd, 1H), 3.3 (m 2H), 2.7-2.5 (m, 1H), 2.4-2.2 (m, 2H), 2.1-2.0 (m, 1H); MH^+ = 386409.

[00166] Example 21: Synthesis of 3-(8-Oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile (62).

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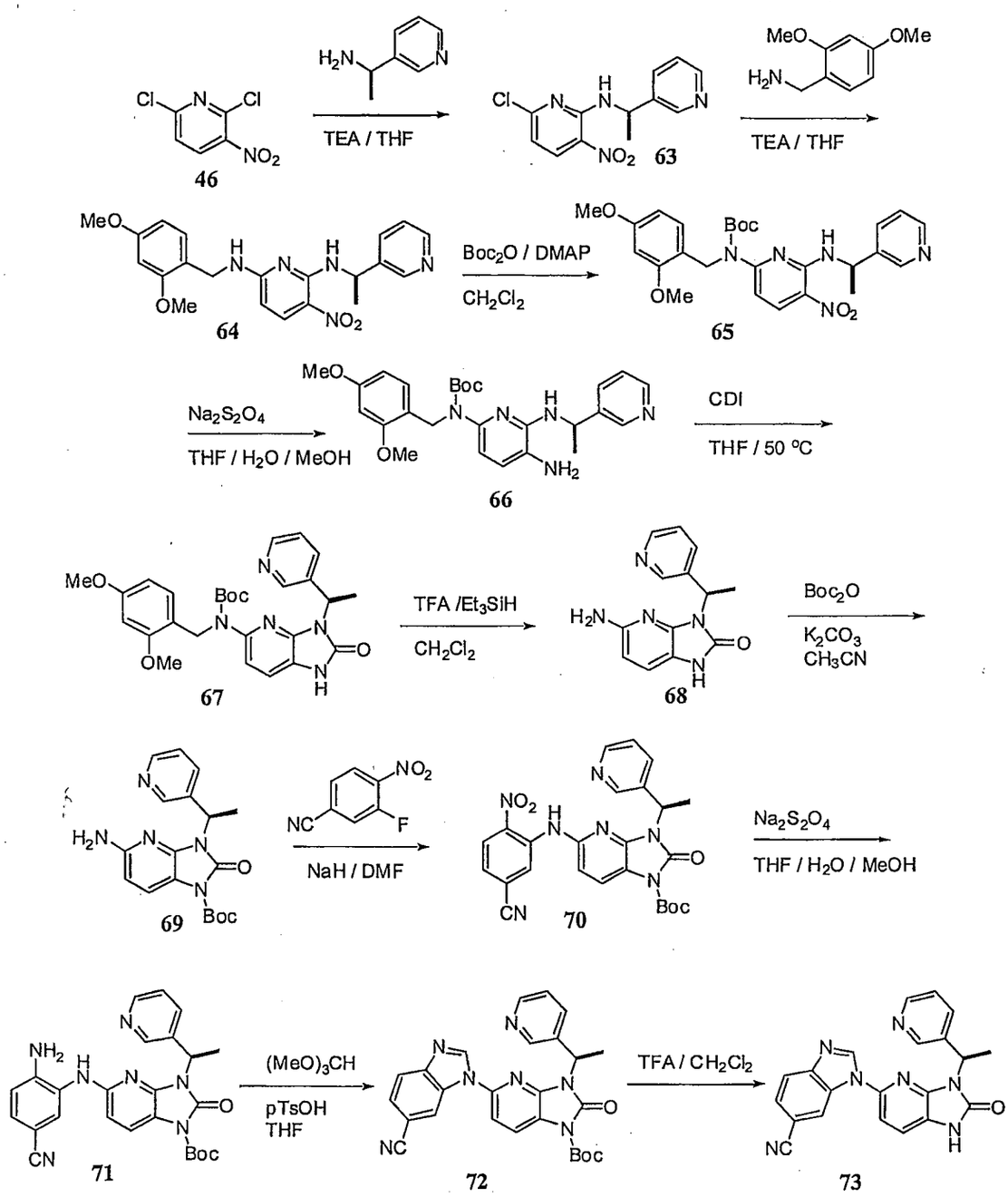


62

[00167] The title compound can be synthesized using the same procedures as described for the synthesis of 3-(9-(2,6-difluorobenzyl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile (**61**, Example 20).

[00168] ^{1}H NMR (d_6-DMSO) 11.71 (s, 1H), 9.34 (s, 1H), 8.94 (d, J = 1.5 Hz, 1H), 8.38 (s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.79 (dd, J = 8.1, 1.5 Hz, 1H), 4.57 (m, 1H), 4.04 (m, 2H), 3.50 (m, 2H), 2.59 (m, 2H), 1.79 (m, 2H); Mass (MH+) 362.1.

[00169] Example 22: Regiospecific synthesis of an oxoimidazopyridine derivative: Synthesis of 3-(2-oxo-3-((R)-1-(pyridin-3-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)-3H-benzo[d]imidazole-5-carbonitrile.



[00170] (R)-N6-(2,4-Dimethoxybenzyl)-3-nitro-N2-(1-(pyridin-3-yl)ethyl)pyridine-2,6-diamine (64). A solution of 2,6-dichloro-5-nitropyridine (**46**) (0.5 g) in THF (20 mL) was cooled to 0 °C and treated with 1.6 mL triethylamine followed by (R)-1-pyridin-3-yl-ethylamine (300 μL). The mixture was stirred for 1.5 h, then warmed to RT and stirred another 20 h. 2,4-Dimethoxybenzylamine (0.8 mL) was added and the mixture was

heated at 50 °C for four hours. The mixture was diluted with ethyl acetate and washed twice with saturated sodium chloride solution. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated. Column chromatography (50 → 100% ethyl acetate in hexanes) provided 761 mg of (R)-N6-(2,4-Dimethoxybenzyl)-3-nitro-N2-(1-(pyridin-3-yl)ethyl)pyridine-2,6-diamine (**64**).

[00171] (R)-tert-Butyl 2,4-dimethoxybenzyl(5-nitro-6-(1-(pyridin-3-yl)ethylamino)pyridin-2-yl)carbamate (65). A solution of (R)-N6-(2,4-dimethoxybenzyl)-3-nitro-N2-(1-(pyridin-3-yl)ethyl)pyridine-2,6-diamine (**64**) (367 mg) in methylene chloride (20 mL) was treated with di-*tert*-butyl dicarbonate (1.0 g) and 4-dimethylaminopyridine (22 mg). The mixture was stirred for 16 h and concentrated *in vacuo*. Column chromatography (50 → 100% ethyl acetate in hexanes) provided 500 mg of (R)-tert-Butyl 2,4-dimethoxybenzyl(5-nitro-6-(1-(pyridin-3-yl)ethylamino)pyridin-2-yl)carbamate (**65**).

[00172] (R)-tert-Butyl 2,4-dimethoxybenzyl(2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)carbamate (67). A solution of (R)-tert-butyl 2,4-dimethoxybenzyl(5-nitro-6-(1-(pyridin-3-yl)ethylamino)pyridin-2-yl)carbamate (500 mg) in THF (25 mL) was treated with an aqueous solution comprised of 2 g of $Na_2S_2O_4$ and 1 g $NaHCO_3$ in 20 mL of water followed by 1 mL of methanol. The mixture was stirred for 30 minutes, then diluted with ethyl acetate and washed with saturated sodium chloride solution. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to provide the intermediate (R)-tert-butyl 2,4-dimethoxybenzyl(5-amino-6-(1-(pyridin-3-yl)ethylamino)pyridin-2-yl)carbamate (**66**). The intermediate was dissolved in THF (50 mL) and treated with 1,1'-carbonyldiimidazole (0.5 g) at 50 °C for 20 h. The mixture was concentrated and purified by column chromatography (2 → 5% MeOH in methylene chloride) to provide 413 mg of (R)-tert-Butyl 2,4-dimethoxybenzyl(2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)carbamate (**67**).

[00173] (R)-tert-Butyl 5-amino-2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (69). A solution of (R)-tert-butyl 2,4-

dimethoxybenzyl(2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)carbamate in methylene chloride (15 mL) was treated with TFA (15 mL) and triethylsilane (1.0 mL) for one hour. The mixture was concentrated to provide the intermediate (R)-5-amino-3-(1-(pyridin-3-yl)ethyl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (**68**), which was dissolved in acetonitrile (50 mL) and stirred vigorously with di-*tert*-butyl dicarbonate (1.0 g) and potassium carbonate (3.0 g) for 2 h. Methylene chloride (200 mL) and water (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with another 100 mL of methylene chloride. The combined organic layers were separated, dried over sodium sulfate, filtered, and concentrated. Column chromatography (2 → 3 → 4% MeOH in methylene chloride) provided 235 mg (R)-tert-Butyl 5-amino-2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**69**).

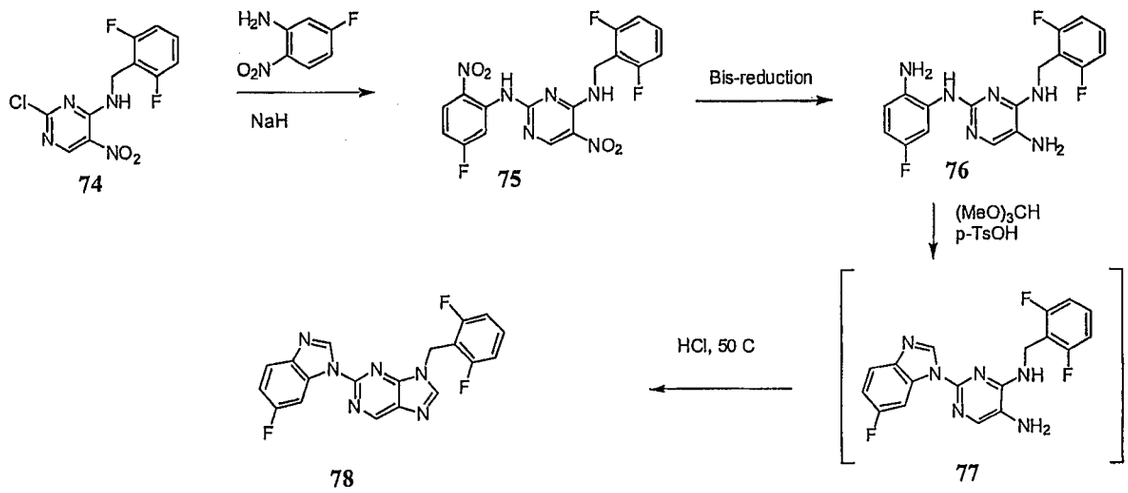
[00174] (R)-tert-Butyl 5-(5-cyano-2-nitrophenylamino)-2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**70**). A solution of (R)-tert-butyl 5-amino-2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (94 mg) and 3-fluoro-4-nitrobenzonitrile (225 mg) in DMF (6 mL) was cooled to -25 °C and treated with NaH (60% w/w in mineral oil, 75 mg) and slowly allowed to warm to -15 °C. The mixture was stirred for four hours between -20 °C and -15 °C, then diluted with EtOAc and quenched with saturated ammonium chloride solution. The organic phase was washed three times with brine, separated, dried over sodium sulfate, filtered, and concentrated. Column chromatography (2% MeOH in methylene chloride) provided 100 mg (R)-tert-Butyl 5-(5-cyano-2-nitrophenylamino)-2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**70**).

[00175] tert-Butyl 5-(6-cyano-1H-benzo[d]imidazol-1-yl)-2-oxo-3-((R)-1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**72**). A solution of (R)-tert-butyl 5-(5-cyano-2-nitrophenylamino)-2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**70**) (100 mg) in THF (5 mL) was treated with an aqueous solution comprised of 0.5 g of $Na_2S_2O_4$ and 0.25 g $NaHCO_3$ in 5 mL of water. The mixture went quickly from a red color to a slightly yellow color, which indicated reduction of the nitro group. The mixture was diluted with ethyl acetate and

washed with saturated sodium chloride solution. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to provide the intermediate (R)-tert-butyl 5-(2-amino-5-cyanophenylamino)-2-oxo-3-(1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**71**). The intermediate was dissolved in THF (5 mL), DMF (1 mL), and trimethylorthoformate (2 mL). The mixture was treated with 10 mg of p-toluenesulfonic acid and stirred for 20 h. The mixture was diluted with ethyl acetate and washed once with saturated sodium bicarbonate and twice with saturated NaCl solution. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated. Column chromatography (2% MeOH in methylene chloride) provided 57 mg tert-Butyl 5-(6-cyano-1H-benzo[d]imidazol-1-yl)-2-oxo-3-((R)-1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**72**).

[00176] 3-(2-oxo-3-((R)-1-(pyridin-3-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)-3H-benzo[d]imidazole-5-carbonitrile (73). A solution of tert-butyl 5-(6-cyano-1H-benzo[d]imidazol-1-yl)-2-oxo-3-((R)-1-(pyridin-3-yl)ethyl)-2,3-dihydroimidazo[4,5-b]pyridine-1-carboxylate (**72**) (57 mg) in methylene chloride (1 mL) was treated with TFA (1 mL) for one hour. The mixture was concentrated and the resulting TFA salt was converted to the HCl salt by dissolving it in 5 mL EtOH and adding 0.5 mL of conc. HCl, then concentrating the solution *in vacuo*. The process was repeated and the resulting residue was dissolved in a minimum amount of methanol and triturated with the addition of ethyl ether. After 3 triturations, 3-(2-oxo-3-((R)-1-(pyridin-3-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-5-yl)-3H-benzo[d]imidazole-5-carbonitrile (**73**) HCl salt (39 mg) was isolated as a tan colored solid: ^{1}H-NMR (CD_3OD) δ 9.9 (br s, 1H), 9.2 (s, 1H), 9.0 (m, 2H), 8.5 (s, 1H), 8.3 (m, 1H), 8.2 (m, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 6.3 (q, 1H), 2.3 (d, 3H).

[00177] Example 23: Regiospecific synthesis: Synthesis of 9-(2,6-Difluorobenzyl)-2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9*H*-purine (**78**)



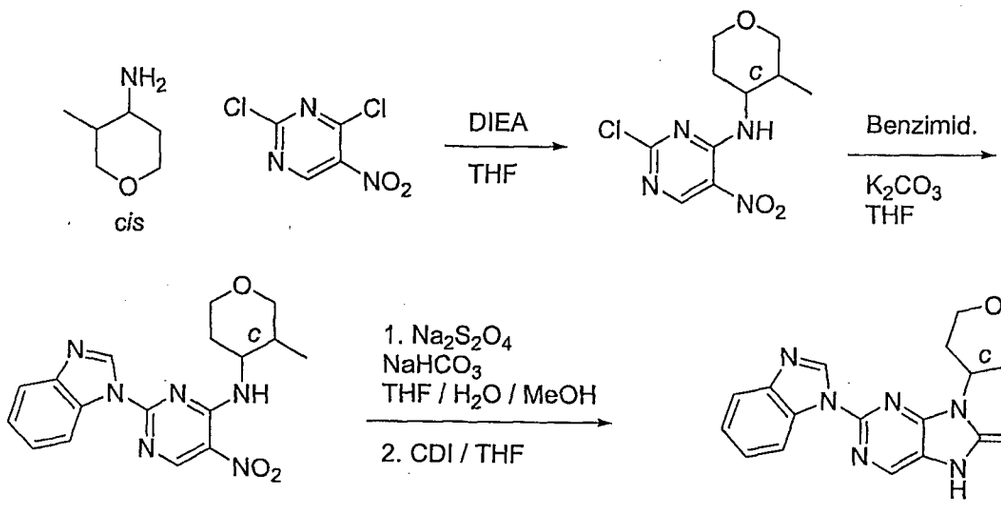
74 75 76 77 78

[00178] ***N*^{4}-(2,6-Difluorobenzyl)-*N*^{2}-(5-fluoro-2-nitrophenyl)-5-nitropyrimidine-2,4-diamine (75).** Under an argon atmosphere, sodium hydride (100 mg) was added to a solution of N-(2,6-difluorobenzyl)-2-chloro-5-nitropyrimidin-4-amine (150 mg) and 5-fluoro-2-nitroaniline (78 mg) in THF (10 mL) at RT. The mixture was stirred for 30 min, quenched via the addition of sat. aq. NH_4Cl, extracted with DCM and purified by preparative HPLC to give a low yield of *N*^{4}-(2,6-difluorobenzyl)-*N*^{2}-(5-fluoro-2-nitrophenyl)-5-nitropyrimidine-2,4-diamine (**75**) (24 mg), $MH^+ = 421$.

[00179] 9-(2,6-Difluorobenzyl)-2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9*H*-purine (78). A freshly prepared solution of sodium hydrosulfite (tech, 100 mg) and sodium bicarbonate (50 mg) in H_2O (5 mL) was added to a solution of *N*^{4}-(2,6-difluorobenzyl)-*N*^{2}-(5-fluoro-2-nitrophenyl)-5-nitropyrimidine-2,4-diamine (**75**) (24 mg) in THF (5 mL). The mixture was stirred vigorously for 30 min and extracted with DCM (3x). The combined organics were washed with brine, dried, filtered and concentrated to yield the intermediate *N*^{4}-(2,6-difluorobenzyl)-*N*^{2}-(2-amino-5-fluorophenyl)pyrimidine-2,4,5-triamine (**76**) for use in the next step. A catalytic amount of *para*-toluene sulfonic acid monohydrate was added to a solution of the intermediate and trimethyl orthoformate (1 mL) in MeOH (2 mL), after 2 hr conc. HCl (1 mL) was added and the mixture was heated at 50 °C for 4 hr. The reaction solvents were removed and the crude material was purified via preparative HPLC to give 9-(2,6-Difluorobenzyl)-2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9*H*-purine (**78**) as the TFA salt in low yield (0.8 mg) $MH^+ = 404$,

^{1}H NMR (5 % $CD_3OD/CDCl_3$) δ 9.1 (s, 1H), 9.0 (s, 1H), 8.3 (d, 1H), 8.2 (s, 1H), 7.6 (m, 1H), 7.0 (t, 1H), 6.9 (m, 2H), 5.5 (s, 2H) ppm, ^{19}F NMR δ-76.6 (s, TFA), -114.5 (m), -117.1 (m).

[00180] Example 24. Synthesis of 2-(1H-Benzo[d]imidazol-1-yl)-9-(*cis*-3-methyl-tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one.



[00181] **2-Chloro-N-(*cis*-3-methyl-tetrahydro-2H-pyran-4-yl)-5-nitropyrimidin-4-amine.** To a suspension of 0.24 g of the hydrochloride salt of *cis*-3-methyl-tetrahydro-2H-pyran-4-amine (WO 2004/041161) and DIEA (1.5 mL) in THF (10 mL) at -78 °C was added 2,4-dichloro-5-nitropyrimidine (0.72 g). The mixture was allowed to slowly reach room temperature and stirred for 16 hours. The mixture was diluted with EtOAc and washed 3 times with brine. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. Column chromatography (20 → 40% EtOAc / hexanes) provided 289 mg of the title compound.

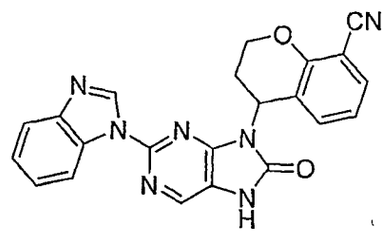
[00182] **2-(1H-Benzo[d]imidazol-1-yl)-N-(*cis*-3-methyl-tetrahydro-2H-pyran-4-yl)-5-nitropyrimidin-4-amine.** To a solution of 2-chloro-N-(*cis*-3-methyl-tetrahydro-2H-pyran-4-yl)-5-nitropyrimidin-4-amine (115 mg) in acetonitrile (5 mL) was added potassium carbonate (300 mg) and benzimidazole (150 mg). The mixture was stirred at 70 °C for 2.5 hours. After diluting with 70 mL EtOAc, the mixture was washed with

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brine, dried over sodium sulfate, and concentrated *in vacuo*. Column chromatography (50 → 100% EtOAc / hexanes) provided 99 mg of the title compound.

[00183] 2-(1H-Benzo[d]imidazol-1-yl)-9-(*cis*-3-methyl-tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one. To a solution of 2-(1H-benzo[d]imidazol-1-yl)-N-(*cis*-3-methyl-tetrahydro-2H-pyran-4-yl)-5-nitropyrimidin-4-amine (51 mg) in THF (10 mL) was added a solution of sodium hydrosulfite (300 mg) and sodium bicarbonate (150 mg) in water (10 mL). The mixture briefly became blue followed by colorless. Methanol (1 mL) was added to maintain the homogeneity of the solution. The mixture was diluted with 70 mL EtOAc and washed twice with brine. The aqueous washes were extracted with another 50 mL of EtOAc and then the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 2-(1H-benzo[d]imidazol-1-yl)-N4-(*cis*-3-methyl-tetrahydro-2H-pyran-4-yl)pyrimidine-4,5-diamine. The diamine intermediate was dissolved in THF (5 mL) and treated with 1,1'-carbonyldiimidazole (80 mg) at 50 °C for 16 hours. The mixture was diluted with 50 mL EtOAc and washed 3 times with brine. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. Column chromatography (2 → 4% MeOH / DCM) provided 19.3 mg of the title compound. ^{1}H-NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 8.9 (s, 1H), 8.5 (d, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.4 (t, 1H), 7.3 (t, 1H), 4.7 (m, 1H), 4.2 (d(br), 1H), 3.9 (d, 1H), 3.7 (d, 1H), 3.5 (m, 2H), 2.3 (t(br), 1H), 1.8 (d(br), 1H), 1.2 (d, 3H).

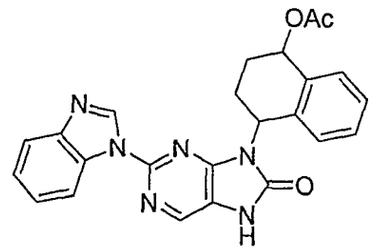
[00184] Synthesis of 4-(2-(1H-Benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile.



[00185] The title compound was synthesized from 4-amino-3,4-dihydro-2H-chromene-8-carbonitrile via the procedure described in Example 24. ^{1}H NMR (300 MHz, d_6-

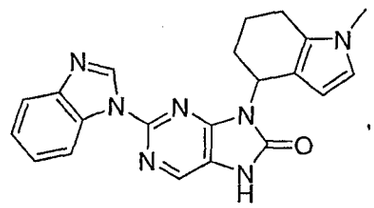
DMSO) δ 8.87 (s, 1H), 8.57 (s, 1H), 7.70 (m, 3H), 7.31 (m, 3H), 6.94 (t, J = 7.8 Hz, 1H), 5.90 (m, 1H), 4.61 (m, 2H), 2.73 (m, 1H), 2.33 (m, 1H); Mass (MH+) 410.1.

[00186] Synthesis of *cis/trans*-4-(2-(1H-Benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)-1,2,3,4-tetrahydronaphthalen-1-yl acetate.



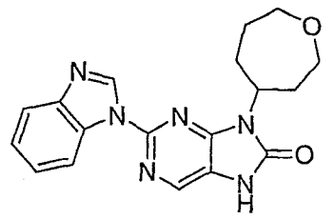
[00187] The title compound was synthesized from 4-amino-1,2,3,4-tetrahydronaphthalen-1-yl acetate via the procedure described in Example 24. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (s, 0.66H), 10.48 (s, 0.34H), 8.87 (s, 0.66H), 8.83 (s, 0.34H), 8.30 (s, 0.66H), 8.27 (s, 0.34H), 7.76-7.02 (m, 8H), 6.35 (m, 0.34H), 6.17 (m, 0.66H), 5.93 (s, 0.34H), 5.79 (m, 0.66H), 2.90-2.01 (m, 7H); Mass (MH+) 441.0.

[00188] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-4-yl)-7*H*-purin-8(9*H*)-one.



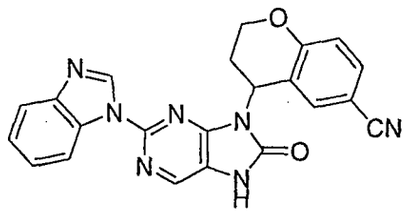
[00189] The title compound was synthesized from 1-methyl-4,5,6,7-tetrahydro-1H-indol-4-amine via the procedure described in Example 24. ^{1}H NMR (CD_3OD) δ 8.90 (s, 1H), 8.25 (s, 1H), 7.88 (m, 1H), 7.68 (m, 1H), 7.32 (m, 2H), 6.51 (d, J = 2.7 Hz, 1H), 5.66 (m, 2H), 3.65 (s, 3H), 2.80 (m, 2H), 2.46 (s, 1H), 2.19 (m, 2H), 1.96 (m, 1H); Mass (MH+) 386.0.

[00190] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(oxepan-4-yl)-7*H*-purin-8(9*H*)-one.



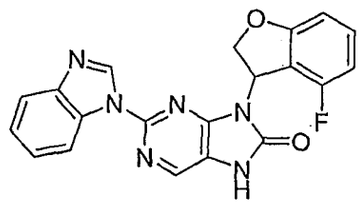
[00191] The title compound was synthesized from oxepan-4-amine via the procedure described in Example 24. ^{1}H-NMR ($CDCl_3$) δ 9.0 (s, 1H), 8.5 (d, 1H), 8.1 (s, 1H), 7.7 (d, 1H), 7.3 (m, 2H), 4.6 (t, 1H), 3.9 (m, 2H), 3.8 (m, 2H), 2.7 (m, 2H), 2.0 (m, 4H) ppm.

[00192] Synthesis of 4-(2-(1*H*-Benzo[*d*]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)chroman-6-carbonitrile.



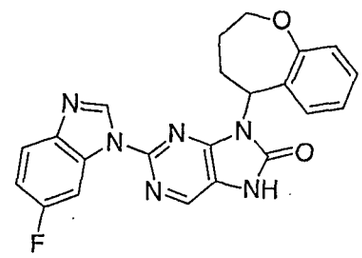
[00193] The title compound was synthesized from 4-amino-3,4-dihydro-2H-chromene-6-carbonitrile via the procedure described in Example 24. ^{1}H-NMR of TFA salt (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 9.2 (s, 1H), 8.4 (s, 1H), 8.0 (d, 1H), 7.9 (d, 1H), 7.4-7.6 (m, 3H), 7.1-7.2 (m, 2H), 5.8-6.0 (m, 1H), 4.6-4.7 (m, 1H), 4.4-4.5 (m, 1H), 2.8-3.0 (m, 1H), 2.2-2.4 (m, 1H).

[00194] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(4-fluoro-2,3-dihydrobenzofuran-3-yl)-7*H*-purin-8(9*H*)-one.



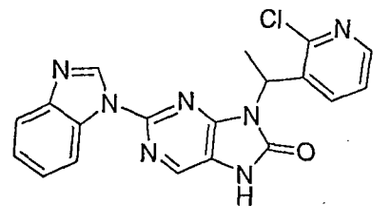
[00195] The title compound was synthesized from 4-fluoro-2,3-dihydrobenzofuran-3-amine (prepared in example 37) via the procedure described in Example 24. ^{1}H-NMR (300 MHz, $CDCl_3$+5%CD_3OD) δ 8.7 (s, 1H), 8.1-8.2 (m, 1H), 8.1 (s, 1H), 7.6-7.7 (m, 1H), 7.1-7.3 (m, 3H), 6.7 (d, 1H), 6.5 (d, 1H), 6.3-6.4 (m, 1H), 4.8-4.9 (m, 2H).

[00196] Synthesis of 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-(2,3,4,5-tetrahydrobenzo[*b*]oxepin-5-yl)-7*H*-purin-8(9*H*)-one.



[00197] The title compound was synthesized from 2,3,4,5-tetrahydrobenzo[*b*]oxepin-5-amine (obtained from the corresponding ketone (J. Med. Chem., 2004, 47, 5612) using the same procedures outlined for the 4-aminochromanes) via the procedure described in Example 24. ^{1}H-NMR (300 MHz, $CDCl_3$+5%CD_3OD) δ 8.8 (s, 1H), 8.2 (s, 1H), 8.0 (dd, 1H), 7.6-7.7 (m, 1H), 6.95-7.2 (m, 3H), 6.9 (t, 1H), 6.6 (d, 1H), 5.9 (d, 1H), 4.4-4.5 (m, 1H), 3.7-3.9 (m, 1H), 2.8-3.0 (m, 1H), 2.0-2.3 (m, 3H).

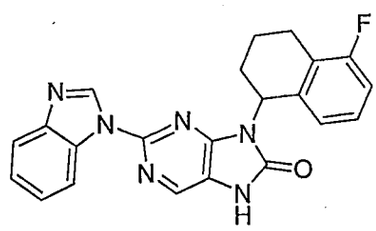
[00198] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(1-(2-chloropyridin-3-yl)ethyl)-7*H*-purin-8(9*H*)-one.



[00199] The title compound was synthesized from 3-(α-aminoethyl)-2-chloropyridine via the procedure described in Example 24. ^{1}H-NMR ($CDCl_3$) δ 8.8 (s, 1H), 8.4 (d, 1H), 8.3 (d, 1H), 8.2 (d, 1H), 8.1 (s, 1H), 7.7 (d, 1H), 7.3 (m, 3H), 3.4 (m, 1H), 2.0 (d, 3H), ppm.

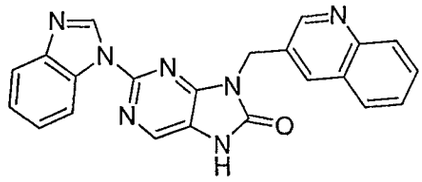
71

[00200] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(5-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)-7*H*-purin-8(9*H*)-one.



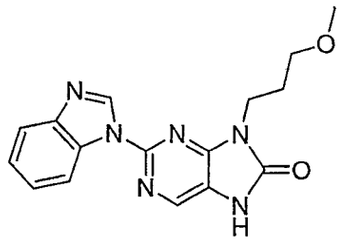
[00201] The title compound was synthesized from 5-fluoro-1,2,3,4-tetrahydronaphthalen-1-amine via the procedure described in Example 24. ^{1}H-NMR ($CDCl_3$) δ 8.7 (s, 1H), 8.1 (s, 1H), 7.6 (d, 1H), 7.5 (d, 1H), 7.2 (q, 2H), 6.9 (m, 2H), 6.7 (d, 1H), 5.7 (m, 1H), 3.3 (s, 2H), 2.8 (m, 2H), 2.4 (q, 1H), 2.1 (m, 1H), 1.8 (m, 1H), ppm.

[00202] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(quinolin-3-ylmethyl)-7*H*-purin-8(9*H*)-one.



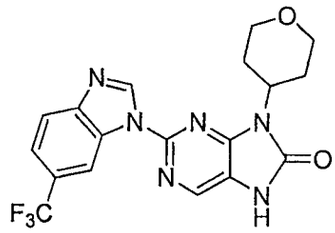
[00203] The title compound was synthesized from 3-aminomethylquinoline via the procedure described in Example 24. ^{1}H-NMR ($CDCl_3$) δ 9.8 (s, 1H), 9.4 (s, 1H), 8.9 (s, 1H), 8.6 (d, 1H), 8.3 (m, 2H), 8.1 (d, 1H), 7.9 (m, 2H), 7.8 (d, 1H), 7.5 (t, 2H), 5.5 (s, 2H) ppm.

[00204] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(3-methoxypropyl)-7*H*-purin-8(9*H*)-one.



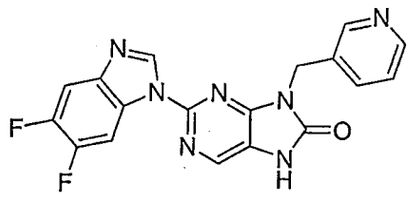
[00205] The title compound was synthesized from 3-methoxypropan-1-amine via the procedure described in Example 24. ^{1}H NMR (CD_3OD) δ9.71 (s, 1H), 8.81 (d, 1H), 8.30 (s, 1H), 7.83 (d, 1H), 7.57 (m, 2H), 4.15 (t, 2H), 3.50 (t, 2H), 3.28 (s, 3H), 2.13 (m, 2H); MS (MH^+) 325.2.

[00206] Synthesis of 9-(Tetrahydro-2H-pyran-4-yl)-2-(6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)-7H-purin-8(9H)-one.



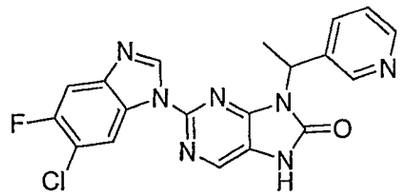
[00207] The title compound was synthesized from 3-methoxypropan-1-amine via the procedure described in Example 24. ^{1}H NMR (CD_3OD + $CHCl_3$) δ9.49 (s, 1H), 9.04 (s, 1H), 8.33 (s, 1H), 7.94 (d, 1H), 7.72 (m, 1H), 4.67 (m, 1H), 4.17 (m, 2H), 3.61 (m, 2H), 2.81 (m, 2H), 1.85 (m, 2H); MS (MH^+) 405.1.

[00208] Synthesis of 2-(5,6-Difluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-(pyridin-3-ylmethyl)-7*H*-purin-8(9*H*)-one.



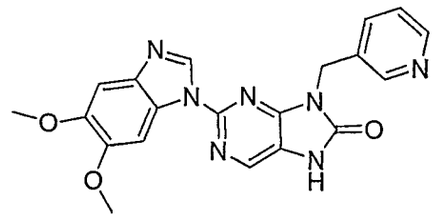
[00209] The title compound was synthesized from 5,6-difluoro-1H-benzo[*d*]imidazole (Example 4) via the procedure described in Example 24. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.2 (s, 1H), 9.0 (br, 1H), 8.7 (br, 1H), 8.6 (d, 1H), 8.4 (dd, 1H), 8.3 (s, 1H), 7.9 (dd, 1H), 7.6 (m, 2H), 5.4 (s, 2H).

[00210] Synthesis of 2-(6-Chloro-5-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-(1-(pyridin-3-yl)ethyl)-7*H*-purin-8(9*H*)-one.



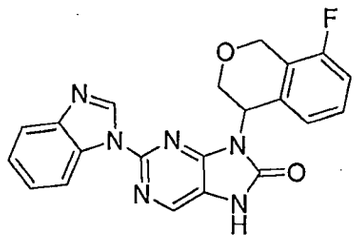
[00211] The title compound was synthesized from 6-chloro-5-fluorobenzimidazole via the procedure described in Example 24. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.2 (bs, 1H), 9.0 (m, 1H), 8.9-8.5 (m, 2H), 8.4 (m, 2H), 7.9 (m, 2H), 7.7 (m, 1H), 6.2 (q, 1H), 2.2 (d, 3H).

[00212] Synthesis of 2-(5,6-Dimethoxy-1*H*-benzo[*d*]imidazol-1-yl)-9-(pyridin-3-ylmethyl)-7*H*-purin-8(9*H*)-one.

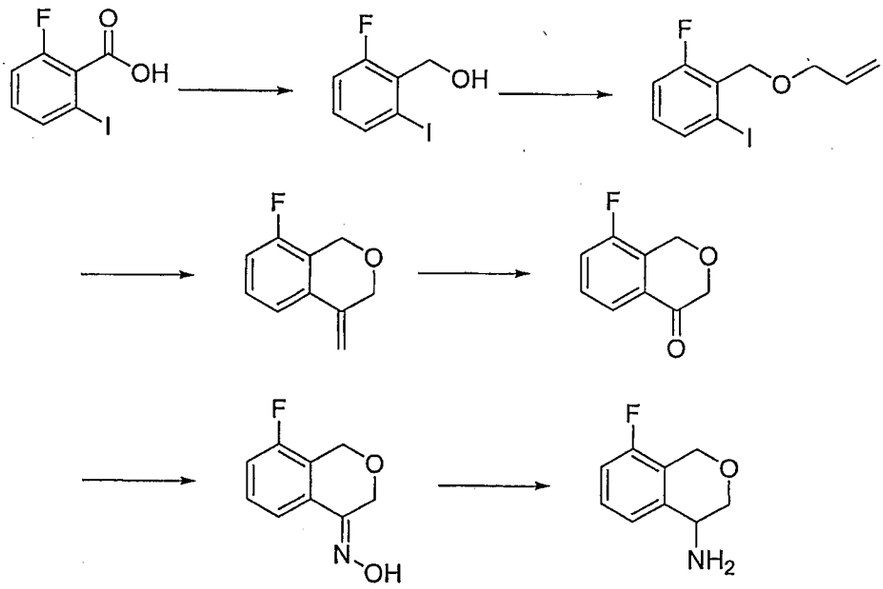


[00213] The title compound was synthesized from 5,6-dimethoxy-1*H*-benzo[*d*]imidazole via the procedure described in Example 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.6 (s, 1H), 8.5(S, 1H), 8.4 (S, 1H), 8.0 (s, 1H), 7.9 (s, 1H), 7.5 (d, 1H), 7.3 (d, 1H), 6.9 (t, 1H), 4.8 (s, 2H), 3.7 (s, 6H).

[00214] Procedure for the synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(8-fluoroisochroman-4-yl)-7*H*-purin-8(9*H*)-one.



[00215] 8-Fluoro-3,4-dihydro-1H-isochromen-4-amine.



[00216] **(2-Fluoro-6-iodophenyl)methanol.** To a stirred solution of 2-fluoro-6-iodobenzoic acid (10mmol) in THF (6.5mL) and trimethylborate (3.25mL) was added borane dimethylsulfide (12mmol) slowly, maintaining the internal temperature at 20-25 °C. Stirring was continued for an additional 16 h at room temperature and then methanol (1.44mL) was added cautiously.The resulted solution was evaporated *in vacuo* to offer 2.5 g of the title compound as a pale yellow oil.

[00217] **2-(Allyloxymethyl)-1-fluoro-3-iodobenzene.** To a solution of (2-fluoro-6-iodophenyl)methanol (10 mmol) in 50 mL of THF was added NaH (12 mmol) in small portions at room temperature. After the addition, allylbromide (12 mmol) was added slowly via syringe. The reaction mixture was stirred 16 hours at room temperature. The resulting white heterogeneous mixture was quenched with water and then diluted with 100 mL of Et_2O, followed by washing with water and brine. The organic layer

was dried over $MgSO_4$ and then concentrated to dryness *in vacuo* to offer 2.8g of the title compound.

[00218] 8-Fluoro-4-methylene-3,4-dihydro-1H-isochromene. 2-(Allyloxymethyl)-1-fluoro-3-iodobenzene (1g) was dissolved in 20mL of CH_3CN and 2.4 mL of Et_3N. The reaction solution was vacuum degassed three times, followed by the addition of $Pd(OAc)_2$ (37.6mg) and PPh_3 (89.8mg). The resulting mixture was heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and diluted with Et_2O. The organic layer was washed with 1N HCl, 10% aqueous $NaHCO_3$, brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated to dryness to offer a brown oil, which was purified by flash chromatography to offer 200 mg of the title compound.

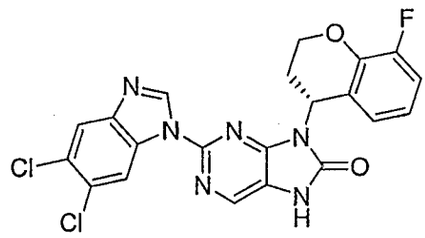
[00219] 8-Fluoro-1H-isochromen-4(3H)-one. 8-Fluoro-4-methylene-3,4-dihydro-1H-isochromene (400 mg) was dissolved in a solution of 1:1 MeOH/DCM (50 mL) and 1mL of pyridine added. The mixture was chilled to -78℃ and ozone was bubbled through the mixture for 40 min. The reaction monitored by TLC. The mixture was purged with nitrogen at -78℃ for 10 min and then treated with PPh_3. After concentration, the resulting residue was purified by preparative TLC to offer 300 mg of the title compound.

[00220] 8-Fluoro-3,4-dihydro-1H-isochromen-4-amine. The title compound was prepared from 8-fluoro-1H-isochromen-4(3H)-one via the procedure described in Example 29. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.4 (m, 1H), 7.3 (d, 1), 7.2 (m, 1H), 5.0 (d, 1H), 4.7 (d, 1H), 4.4 (s, 1H), 4.2 (d, 1H) 3.9 (d, 1H) ppm.

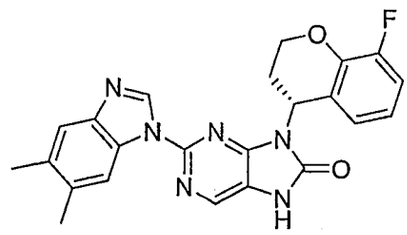
[00221] 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(8-fluoroisochroman-4-yl)-7*H*-purin-8(9*H*)-one. The title compound was synthesized from 8-fluoroisochroman-4-amine via the procedure described in Example 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.7 (bs,

1H), 8.2 (s, 1H), 7.6 (m, 2H), 7.3-6.9 (m, 4H), 6.8 (d, 1H), 5.8 (t, 1H), 5.0 (s, 2H), 4.2 (m, 2H).

[00222] Example 25.

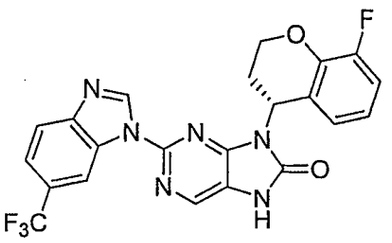


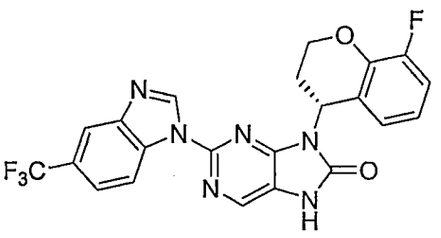
[00223] 2-(5,6-Dichloro-1H-benzo[d]imidazol-1-yl)-9-((R)-8-fluorochroman-4-yl)-7H-purin-8(9H)-one. A solution of (R)-2-chloro-N-(8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine in acetonitrile was treated with 5,6-dichlorobenzimidazole and potassium carbonate. The mixture was stirred at reflux for 6 hours, cooled to room temperature, diluted with 150 mL of EtOAc, and washed twice with 30 mL portions of water. The organic layer was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (2% MeOH/DCM) gave the intermediate nitropyrimidinamine. The title compound was synthesized from the intermediate nitropyrimidinamine via the procedures described in Example 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.7 (s, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.8 (t, 1H), 7.0 (t, 1H), 6.6 (m, 2H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 3.0 (m, 1H), 2.3 (m, 1H).



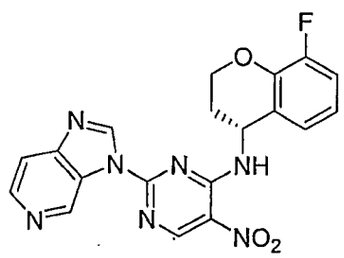
[00224] 2-(5,6-Dimethyl-1H-benzo[d]imidazol-1-yl)-9-((R)-8-fluorochroman-4-yl)-7H-purin-8(9H)-one. The title compound was synthesized from 5,6-dichlorobenzimidazole via the procedures described in Example 25. ^{1}H-NMR (300

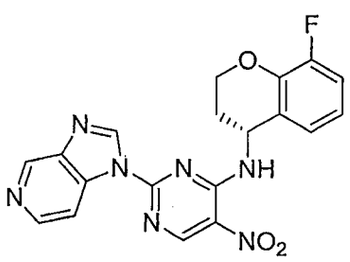
MHz, $CDCl_3$) δ 9.6 (s, 1H), 8.8 (s, 1H), 8.3 (s, 1H), 8.0 (s, 1H), 7.6 (s, 1H), 7.0 (t, 1H), 6.7 (m, 1H), 5.9 (t, 1H), 4.7 (m, 1H), 4.5 (m, 1H), 3.2 (m, 2H), 2.4 (d, 6H).





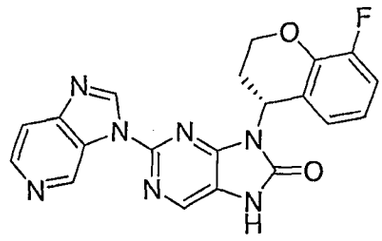
[00225] 9-((R)-8-Fluorochroman-4-yl)-2-(6-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)-7H-purin-8(9H)-one and 9-((R)-8-fluorochroman-4-yl)-2-(5-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)-7H-purin-8(9H)-one. The title compound was synthesized from 5-trifluoromethylbenzimidazole (US 2004/0087601) via the procedures described in Example 25. Purification by column chromatography (2% MeOH/DCM) eluted the 6-trifluoromethyl isomer first (^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.8 (d, 2H), 8.4 (s, 1H), 7.9 (d, 1H), 7.6 (d, 2H), 7.0 (t, 1H), 6.7 (m, 2H), 5.9 (t, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 3.0 (m, 1H), 2.4 (m, 1H).) followed by the 5-trifluoromethyl isomer (^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.4 (s, 1H), 8.1 (s, 1H), 8.0 (d, 1H), 7.6 (d, 2H), 7.0 (m, 1H), 6.8 (m, 2H), 5.9 (t, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 2.9 (m, 1H), 2.4 (m, 1H).



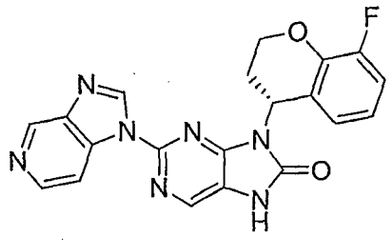


[00226] N-((R)-8-Fluorochroman-4-yl)-2-(3H-imidazo[4,5-c]pyridin-3-yl)-5-nitropyrimidin-4-amine and N-((R)-8-fluorochroman-4-yl)-2-(1H-imidazo[4,5-

c]pyridin-1-yl)-5-nitropyrimidin-4-amine. The title compound was synthesized from 5-azabenzimidazole via the procedure described in Example 25. Purification by column chromatography (1% MeOH / DCM) provided N-((R)-8-fluorochroman-4-yl)-2-(3H-imidazo[4,5-c]pyridin-3-yl)-5-nitropyrimidin-4-amine as the first eluting isomer: (^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H), 9.4 (s, 1H), 9.2 (s, 1H), 8.9 (d, 1H), 8.6 (d, 1H), 7.8 (d, 1H), 7.1 (m, 2H), 6.9 (m, 1H), 5.8 (q, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.6 (m, 1H), 2.4 (m, 1H).). N-((R)-8-Fluorochroman-4-yl)-2-(1H-imidazo[4,5-c]pyridin-1-yl)-5-nitropyrimidin-4-amine eluted second: (^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 9.2 (s, 1H), 9.1 (s, 1H), 8.9 (d, 1H), 8.6 (d, 1H), 8.4 (d, 1H), 7.1 (m, 2H), 6.9 (m, 1H), 5.7 (q, 1H), 4.5 (m, 1H), 4.4 (m, 1H), 2.6 (m, 1H), 2.4 (m, 1H).).

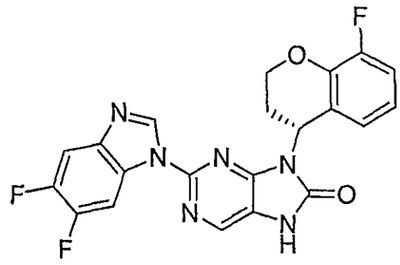


[00227] 9-((R)-8-fluorochroman-4-yl)-2-(3H-imidazo[4,5-c]pyridin-3-yl)-7H-purin-8(9H)-one. The title compound was synthesized from N-((R)-8-fluorochroman-4-yl)-2-(3H-imidazo[4,5-c]pyridin-3-yl)-5-nitropyrimidin-4-amine via the procedures described in Example 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H), 9.4 (s, 1H), 8.6 (d, 1H), 8.3 (m, 2H), 7.0 (t, 1H), 6.7 (m, 2H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (m, 1H).



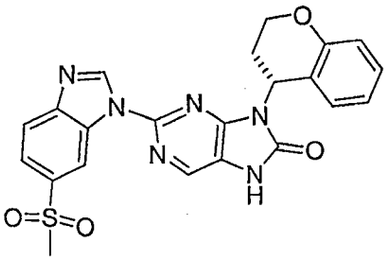
[00228] 9-((R)-8-fluorochroman-4-yl)-2-(1H-imidazo[4,5-c]pyridin-1-yl)-7H-purin-8(9H)-one. The title compound was synthesized from N-((R)-8-fluorochroman-4-yl)-2-(1H-imidazo[4,5-c]pyridin-1-yl)-5-nitropyrimidin-4-amine via the procedures described in Example 24. ^{1}H-NMR (300 MHz, CDCl3) δ 9.3 (d, 2H), 8.4 (d, 1H), 8.3 (d, 2H), 7.0 (t, 1H), 6.7 (m, 2H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (m, 1H).

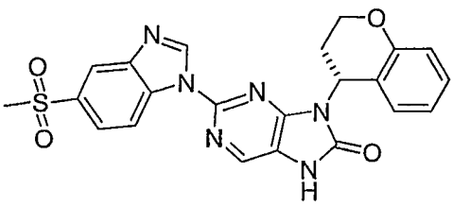
[00229] Synthesis of 2-(5,6-Difluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one.



[00230] The title compound was synthesized from 5,6-difluoro-1H-benzo[*d*]imidazole (Example 4) via the procedure described in Example 25. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.8 (s, 1H), 8.3 (s, 1H), 7.8 (t, 1H), 7.6 (t, 1H), 7.1 (t, 1H), 6.8 (m, 1H), 5.9 (t, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 3.6 (s, 3H), 2.9 (m, 1H), 2.4 (m, 1H) ppm.

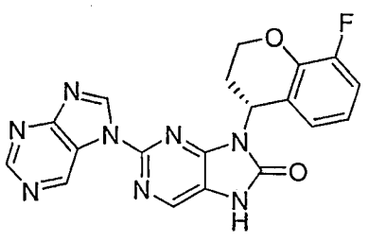
[00231] Synthesis of 9-(*R*)-Chroman-4-yl-2-(6-methanesulfonyl-benzoimidazol-1-yl)-7,9-dihydro-purin-8-one and 9-(*R*)-Chroman-4-yl-2-(5-methanesulfonyl-benzoimidazol-1-yl)-7,9-dihydro-purin-8-one.





[00232] The title compounds were synthesized from 5-methylsulfonylbenzimidazole (prepared as per examples 4 and 5) via the procedure described in Example 25. Purification by column chromatography (2% MeOH / DCM) provided 9-(*R*)-chroman-4-yl-2-(6-methanesulfonyl-benzoimidazol-1-yl)-7,9-dihydro-purin-8-one as the first eluting isomer: ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.8 (s, 1H), 8.3 (s, 1H), 7.9 (d, 2H), 7.2 (t, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (t, 1H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (t, 1H), 3.1 (s, 3H), 2.9 (m, 1H), 2.4 (m, 1H) ppm, and 9-(*R*)-Chroman-4-yl-2-(5-methanesulfonyl-benzoimidazol-1-yl)-7,9-dihydro-purin-8-one as the second eluting isomer ^{1}H-NMR ($CDCl_3$) δ 8.9 (s, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 7.8 (d, 1H), 7.2 (m, 1H), 7.1 (d, 1H), 6.9 (d, 1H), 6.8 (t, 1H), 5.9 (t, 1H), 4.5 (m, 1H), 4.4 (t, 1H), 3.1 (s, 3H), 2.9 (m, 1H), 2.4 (m, 1H) ppm.

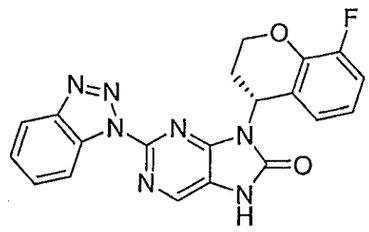
[00233] Synthesis of 9-((*R*)-8-Fluorochroman-4-yl)-2-(7*H*-purin-7-yl)-7*H*-purin-8(9*H*)-one.



[00234] The title compound was synthesized from 7*H*-purine via the procedure described in Example 25. ^{1}H-NMR ($CDCl_3$) δ 9.4 (s, 1H), 9.2 (s, 1H), 9.1 (s, 1H), 8.3

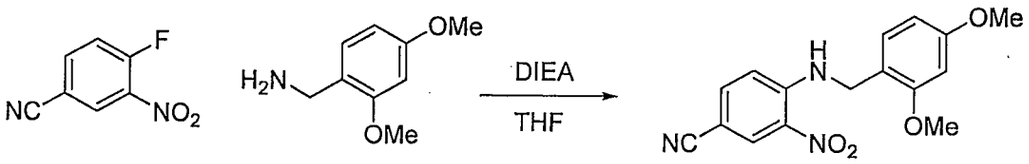
(s, 1H), 7.8 (s, 1H), 7.0 (m, 1H), 6.8 (d, 2H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.9 (m, 1H), 2.4 (m, 1H) ppm.

[00235] Synthesis of 2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one.



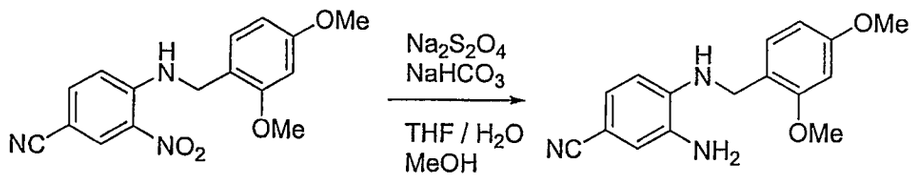
[00236] The title compound was synthesized from 1*H*-benzo[*d*][1,2,3]triazole via the procedure described in Example 25. ^{1}H-NMR (5% CD_3OD in $CDCl_3$) δ 8.4 (br s, 1H), 8.0 (d, 1H), 7.5-7.3 (m, 3H), 7.0-6.9 (m, 1H), 6.7 (m, 2H), 5.9 (dd, 1H), 4.5 (dt, 1H), 4.3 (td, 1H), 2.9-2.8 (m, 1H), 2.4-2.2 (m, 1H) ppm.

[00237] Example 26. Synthesis of 3-(9-((R)-6,8-difluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile:

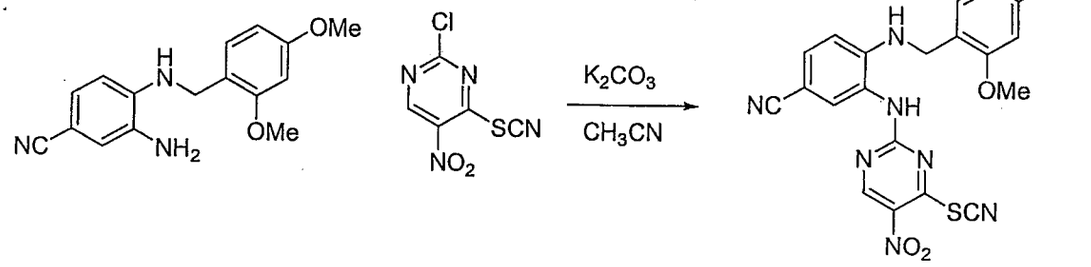


[00238] **4-(2,4-dimethoxybenzylamino)-3-nitrobenzonitrile.** A solution of 4-fluoro-3-nitrobenzonitrile (5.0 g) in THF (100 mL) was treated with DIEA (6.3 mL) and 2,4-dimethoxybenzylamine (5.0 mL), and then stirred for 24 h. The solvent was evaporated and the crude mixture was dissolved in EtOAc (100 mL). The solution was washed once with 1 M HCl and twice with saturated aqueous NaCl (100 mL each). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in*

vacuo. Column chromatography (20% EtOAc / DCM) provided 9.25 g of the title compound.

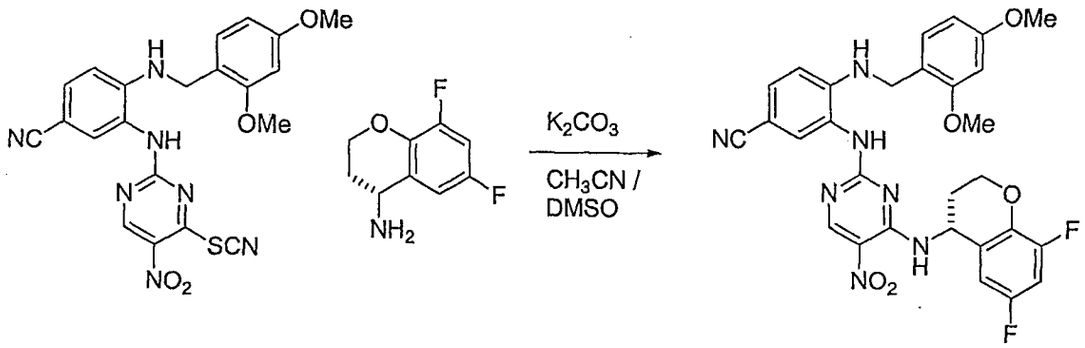


[00239] 4-(2,4-dimethoxybenzylamino)-3-aminobenzonitrile. A solution of 4-(2,4-dimethoxybenzylamino)-3-nitrobenzonitrile (4.54 g) in THF (400 mL) was treated with a solution of sodium hydrosulfite (20 g) and sodium bicarbonate (10 g) in distilled water (350 mL). Enough methanol was immediately added (50 mL) to maintain a homogeneous solution. After 15 minutes, EtOAc (500 mL) and saturated aqueous NaCl (500 mL) were added and the organic layer was separated. The aqueous layer was extracted again with 400 mL EtOAc. The combined organic layers were washed with saturated aqueous NaCl (500 mL) and separated. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 4.33 g of the title compound.

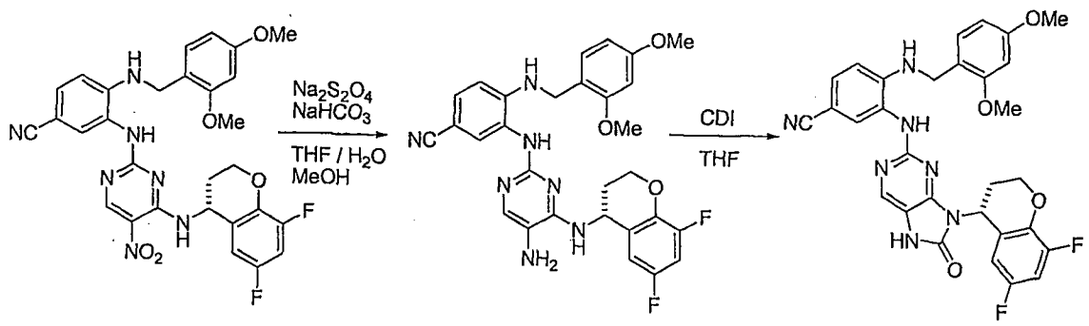


[00240] 4-(2,4-dimethoxybenzylamino)-3-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)benzonitrile. A solution of 4-(2,4-dimethoxybenzylamino)-3-aminobenzonitrile (3.9 g) in acetonitrile (100 mL) was cooled to 0 °C and treated with potassium carbonate (6.3 g) followed by a solution containing 3 g of 2-chloro-5-nitro-4-thiocyanatopyrimidine (WO 2003/032994) in acetonitrile (50 mL). The mixture was

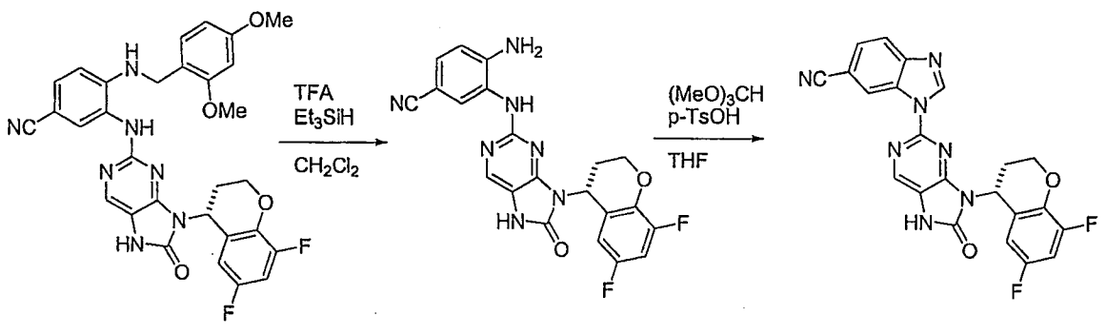
stirred for 30 minutes at 0 °C and 30 minutes at room temperature resulting in the formation of a precipitate. The mixture was quenched at 0 °C by the addition of 4% acetic acid (150 mL) and filtered. The precipitate was swirled in 100 mL acetonitrile and filtered again. The precipitate was washed with acetonitrile, which resulted in the slow dissolution of product into the filtrate. After air-drying, 1.5 g of the title compound remained as the precipitate cake. The filtrate was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (0→20% EtOAc / DCM) and recrystallization from acetonitrile provided 0.415 g of additional title compound.



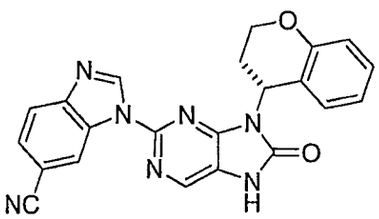
[00241] (R)-4-(2,4-dimethoxybenzylamino)-3-(4-(6,8-difluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)benzonitrile. A partial suspension of 4-(2,4-dimethoxybenzylamino)-3-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)benzonitrile (415 mg) in 40 mL of acetonitrile was treated with a solution of (R)-6,8-difluorochroman-4-amine HCl salt (320 mg) in DMSO (10 mL) followed by potassium carbonate (1.0 g). The mixture was stirred for 24 hours, and then diluted with EtOAc (200 mL). The mixture was washed once with saturated aqueous ammonium chloride (200 mL) and 3 times with saturated aqueous NaCl (200 mL each). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (20→40% EtOAc / hexanes) provided 358 mg of the title compound.



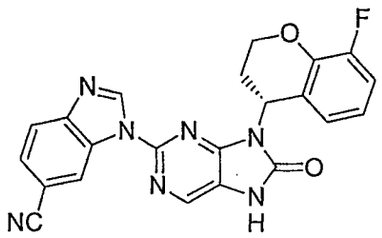
[00242] (R)-4-(2,4-dimethoxybenzylamino)-3-(9-(6,8-difluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-ylamino)benzonitrile. A solution of (R)-4-(2,4-dimethoxybenzylamino)-3-(4-(6,8-difluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)benzonitrile (358 mg) in THF (25 mL) was treated with a solution of sodium hydrosulfite (1.5 g) and sodium bicarbonate (1.5 g) in 20 mL of distilled water. Methanol (5 mL) was added to maintain a homogeneous solution. After 15 minutes, the mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous NaCl (2 X 100 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the intermediate (R)-4-(2,4-dimethoxybenzylamino)-3-(5-amino-4-(6,8-difluorochroman-4-ylamino)pyrimidin-2-ylamino)benzonitrile. The intermediate was dissolved in THF (5 mL) and treated with carbonyldiimidazole (0.55 g) for 16 hours. The mixture was diluted with EtOAc (100 mL) and washed twice with saturated aqueous NaCl (2 X 100 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (2→3% MeOH / DCM) provided 230 mg of the title compound.



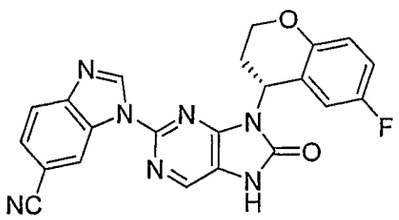
[00243] 3-(9-((R)-6,8-difluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile. A solution of (R)-4-(2,4-dimethoxybenzylamino)-3-(9-(6,8-difluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-ylamino)benzonitrile (230 mg) in DCM (5 mL) was treated with TFA (5 mL) and triethylsilane (1 mL) for 16 h. The mixture was concentrated *in vacuo* to provide the intermediate (R)-4-amino-3-(9-(6,8-difluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-ylamino)benzonitrile. The intermediate was dissolved in 5 mL THF and treated with 3 mL trimethylorthoformate followed by p-toluenesulfonic acid (3 mg). After 1 hour, the mixture was diluted with EtOAc (100 mL) and washed once with saturated aqueous sodium bicarbonate (100 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (50→100% EtOAc / hexanes) provided 78 mg of the title compound. ^{1}H-NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 8.8 (s, 1H), 8.7 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.6 (dd, 1H), 6.8 (td, 1H), 6.4 (dd, 1H), 5.8 (dd, 1H), 4.6 (m, 1H), 4.4 (td, 1H), 2.9 (m, 1H), 2.3 (m, 1H).



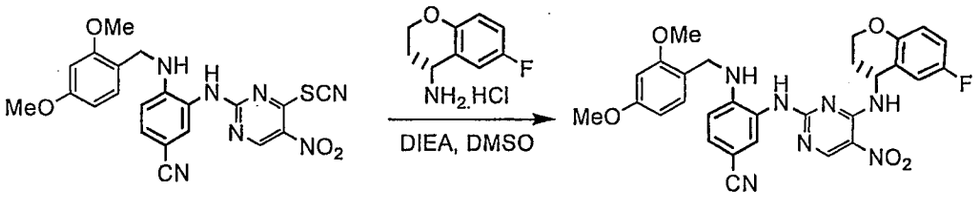
[00244] 3-(9-((R)-chroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile. The title compound was synthesized from (*R*)-chroman-4-amine via the procedures described in Example 26. ^{1}H-NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 8.8 (s, 1H), 8.5 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.5 (dd, 1H), 7.1 (m, 2H), 6.8 (d, 1H), 6.7 (td, 1H), 5.8 (dd, 1H), 4.5 (m, 1H), 4.3 (td, 1H), 2.8 (m, 1H), 2.3 (m, 1H).



[00245] 3-[9-(8-Fluoro-chroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl]-3H-benzoimidazole-5-carbonitrile. The title compound was synthesized from (*R*)-8-fluorochroman-4-amine via the procedures described in Example 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.8 (s, 1H), 8.6 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.0 (t, 1H), 6.6 (m, 2H), 5.8 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (m, 1H).

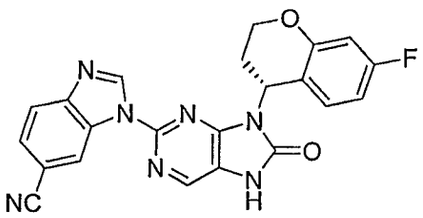


[00246] 3-(9-((R)-6-fluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile. The title compound was synthesized from (*R*)-6-fluorochroman-4-amine via the procedures described in Example 26. ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.86 (s, 1H), 8.41 (s, 1H), 8.18 (s, 1H), 7.72 (d, 1H), 7.51 (d, 1H), 7.0-7.1 (m, 1H), 6.8-6.9 (m, 1H), 6.49 (dd, 1H), 5.76 (br t, 1H), 4.4-4.5 (m, 1H), 4.24 (br t, 1H), 2.7-2.9 (m, 1H), 2.2-2.3 (m, 1H). Conditions for introduction of the chromanyl amine were improved as described below:



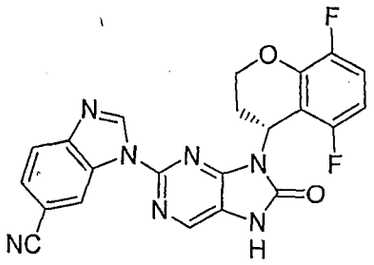
[00247] **(*R*)-4-(2,4-dimethoxybenzylamino)-3-(4-(6-fluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)benzonitrile.** A solution of 4-(2,4-dimethoxybenzylamino)-3-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)benzonitrile (139 mg) in anhydrous DMSO (3 mL) was added to solution of (*R*)-6-fluorochroman-4-amine hydrochloride (79 mg) in anhydrous DMSO (3 mL) and DIEA (0.21 mL), the resulting dark red solution was stirred at RT under an atmosphere of Ar over which time the solution lighten to yellow. Upon completion of the reaction, the mixture was cooled to 0 °C with an ice bath, and water (25 mL) was added (exotherm). The resulting yellow solid was collected via filtration, washed with additional water, air dried, then dissolved in CH_2Cl_2, the organic solution was dried ($MgSO_4$), filtered and evaporated to yield the titled compound (quant.), NMR $CDCl_3$ ^1H δ 9.0 (s, 1H), 8.6(d, 1H), 7.7 (br s, 1H), 7.4 (dd, 1H), 7.1 (d, 1H), 7.0-6.8 (m, 4H), 6.5-6.4 (m, 2H), 5.2 (br s, 1H), 4.3 (s, 2H), 4.2 (br s, 2H), 3.8 (s, 6H), 2.2 (br s, 1H), 1.8 (br s, 1H); ^{19}F δ -123 ppm; $MH^+ = 572$.

[00248] This material was taken on using the same procedures outlined in Example 26 to give 3-(9-((*R*)-6-fluorochroman-4-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile.



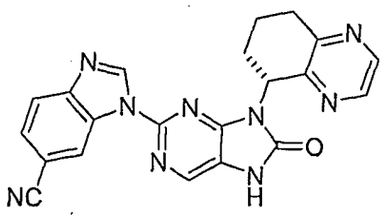
88

[00249] 3-(9-((R)-7-fluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile. The title compound was synthesized from (*R*)-7-fluorochroman-4-amine via the procedures described in Example 26. ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.86 (s, 1H), 8.58 (s, 1H), 8.19 (s, 1H), 7.79 (d, 1H), 7.56 (d, 1H), 6.7-6.9 (m, 2H), 6.4-6.5 (m, 1H), 5.78 (br t, 1H), 4.5-4.6 (m, 1H), 4.32 (br t, 1H), 2.7-2.9 (m, 1H), 2.2-2.4 (m, 1H).



[00250] 3-[9-(5,8-Difluoro-chroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl]-3H-benzoimidazole-5-carbonitrile. The title compound was synthesized from (*R*)-5,8-difluorochroman-4-amine via the procedures described in Example 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.8 (s, 1H), 8.7 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.0 (m, 1H), 6.4 (m, 1H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4(m, 1H), 2.5(m, 2H).

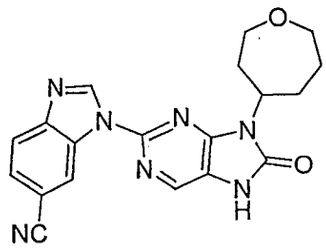
[00251] Synthesis of 3-(8-Oxo-9-((*R*)-5,6,7,8-tetrahydroquinoxalin-5-yl)-8,9-dihydro-7*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile.



[00252] The title compound was synthesized from (*R*)-5,6,7,8-tetrahydroquinoxalin-5-amine (example 34) via the procedure described in Example 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.8 (br, 1H), 8.9 (s, 1H), 8.6 (s, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 8.2 (s,

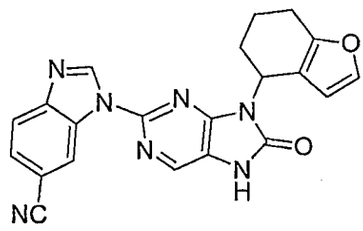
1H), 7.9 (d, 1H), 7.6 (d, 2H), 5.9 (dd, 2H), 3.2-3.5 (m, 2H), 2.8 (q, 1H), 2.3-2.5 (m, 2H), 2.1 (m, 1H).

[00253] Synthesis of 3-(9-Oxepan-4-yl-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzoimidazole-5-carbonitrile.



[00254] The title compound was synthesized from oxepan-4-amine (obtained from oxepan-4-one (Chemische Berichte, 1958, *91*, 1589) via oxime reduction as per example 29) via the procedure described in Example 26. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 9.0 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.6 (d, 1H), 4.7 (t, 1H), 3.8 (m, 6H), 2.7 (m, 2H), 2.0 (m, 2H) ppm.

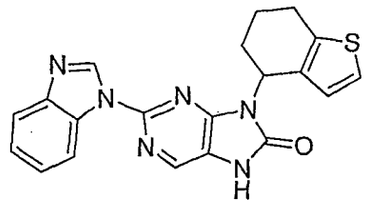
[00255] Synthesis of 3-(8-Oxo-9-(4,5,6,7-tetrahydrobenzofuran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile.



[00256] The title compound was synthesized from 4,5,6,7-tetrahydrobenzofuran-4-amine (obtained via reductive amination of 6,7-dihydrobenzofuran-4(5H)-one as per example 33) via the procedure described in Example 26 ^{1}H-NMR ($CDCl_3$) δ 9.0(s,

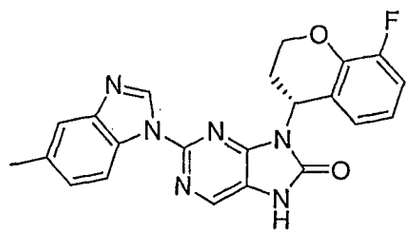
1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.6 (d, 1H), 7.3 (s, 1H), 6.0 (s, 1H), 5.6 (t, 1H), 3.0 (m, 1H), 2.8 (d, 2H), 2.3 (m, 3H), 2.0 (m, 1H) ppm.

[00257] Synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-yl)-7*H*-purin-8(9*H*)-one.



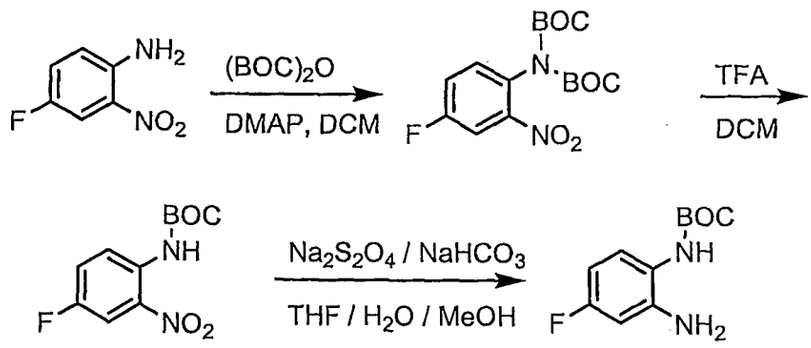
[00258] The title compound was synthesized from 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-amine (obtained via reductive amination of 6,7-dihydrobenzo[b]thiophen-4(5*H*)-one as per example 33) via the procedure described in Example 26 ^{1}H-NMR (5% CD_3OD in $CDCl_3$) δ 9.2 (s, 1H), 8.2 (s, 1H), 7.8-7.7 (m, 2H), 7.4 (m, 2H), 7.0 (d, 1H), 6.6 (d, 1H), 5.7 (dd, 1H), 3.0 (br s, 2H), 2.4-2.0 (m, 4H) ppm.

[00259] Synthesis of 9-((*R*)-8-Fluorochroman-4-yl)-2-(5-methyl-1*H*-benzo[*d*]imidazol-1-yl)-7*H*-purin-8(9*H*)-one.



[00260] The title compound was synthesized from (*R*)-8-fluorochroman-4-amine and 4-fluoro-3-nitrotoluene via the procedures described in Example 26. ^{1}H-NMR ($CDCl_3$) δ 9.0 (s, 1H), 8.2 (s, 1H), 7.6 (d, 1H), 7.5 (s, 1H), 7.1 (d, 1H), 6.9 (m, 2H), 5.8 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (s, 3H), 2.3 (m, 1H) ppm.

[00261] Example 27. Synthesis of 2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluoro-chroman-4-yl)-7*H*-purin-8(9*H*)-one:

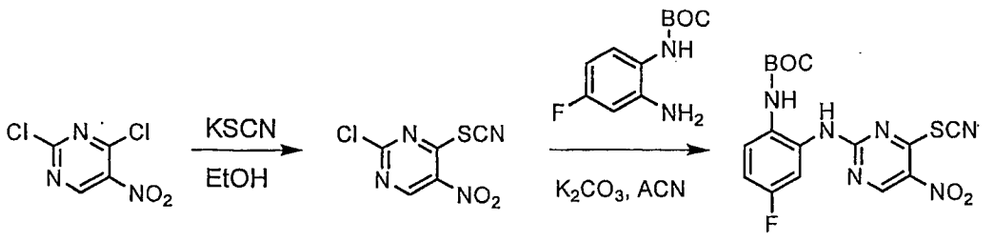


[00262] **4-Fluoro-2-nitro-phenyl di-*tert*-butyl imidodicarbonate.** A catalytic amount of DMAP was added to a mixture of 4-fluoro-2-nitrobenzenamine (0.78 g) and di-*tert*-butyl dicarbonate (2.18 g) in DCM (20 mL) and stirred at room temperature for 15 hr. The mixture was diluted with H_2O and twice extracted with DCM, the combined organics were dried, filtered and evaporated to yield the bis-BOC material (quant). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.8 (dd, 1H), 7.3 (m, 2H), 1.4 (s, 18H).

[00263] ***tert*-Butyl 4-fluoro-2-nitrophenylcarbamate.** (procedure: Connell, R. D.; Rein, T.; Akermark, B.; Helquist, P. J. *J. Org. Chem.* 1988, *53*, 3845) To a stirred solution of the Bis-BOC material in DCM (20 mL) was added TFA (0.58 mL). After 3 hr the reaction was quenched with aq. $NaHCO_3$ (5 mL), brine was added, the mixture separated and extracted with additional DCM. The combined organics were evaporated, purified via column chromatography (eluted with 7.5% EtOAc/Hex) to give the titled product (1.12 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.5 (br 1H), 8.5 (dd, 1H), 7.9 (dd, 1H), 7.3 (m, 1H), 1.5 (s, 9H).

[00264] ***tert*-Butyl 2-amino-4-fluorophenylcarbamate.** To a solution of *tert*-butyl 4-fluoro-2-nitrophenylcarbamate (0.34 g) in THF (30 mL) was added a premixed solution of sodium hydrosulfite (2 g) and sodium bicarbonate (1g) in water (50 mL). MeOH (10 mL) was also added to aid solution of the mixture, which was stirred at

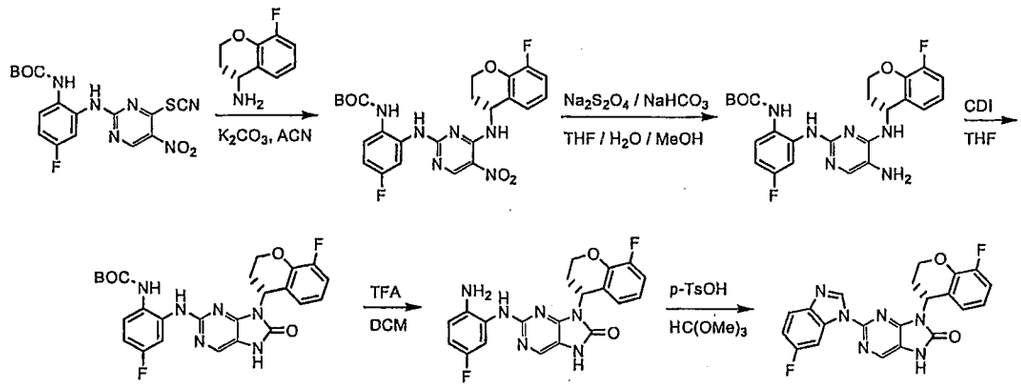
room temperature for 30 min, when sodium chloride was added to saturate the solution. The resultant mixture was extracted with EtOAc (2x). The combined organics were dried, filtered and evaporated to yield the titled compound (quant) that was used as such for the next step. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.5 (dd, 1H), 6.6 (dd, 1H), 6.5 (m, 1H), 6.4 (br 1H), 4.7 (br 2H), 1.5 (s, 9H); MH^+ = 227 (minor) 127 (-BOC), 171 (-*t*Bu).



[00265] 2-Chloro-5-nitro-4-thiocyanatopyrimidine. (compound known, e.g. WO 2003/032994) Potassium thiocyanate (0.97 g, 10 mM) was added to a solution of 2,4-dichloro-5-nitropyrimidine (1.94 g 10, mM) in EtOH (40 mL) cooled to 0 °C via an ice bath. The solution was stirred at 0 °C for 30 min, then the bath was removed and the resulting suspension allowed to come to RT over 60 min, when water (100 mL) was added. The precipitate was collected via filtration, washed with ice cold water, dissolved with DCM, dried ($MgSO_4$), filtered and evaporated to yield the titled compound (1.7 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H).

[00266] *tert*-Butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)phenylcarbamate. Potassium carbonate (207 mg) was added to a stirred solution of 2-chloro-5-nitro-4-thiocyanatopyrimidine (108 mg) and *tert*-butyl 4-fluoro-2-nitrophenylcarbamate (113 mg) in ACN (5 mL) and stirred for 15 hr. The solution was diluted with brine and extracted with EtOAc (2x). The combined organics were evaporated and purified via column chromatography, elution with 30 % EtOAc/Hex gave the titled compound (144 mg, 71 % yield). ^{1}H-NMR (300 MHz, DMSO-d6) δ

10.5 (br s, 1H), 9.3 (br s, 1H), 8.9 (br s, 1H), 7.7-7.4 (m, 2H), 7.1 (br s, 1H), 1.5 (s, 9H), 1.5 (s, 9H); MH^+ = 407, 307 (-BOC), 351 (-*t*Bu).



[00267] (*R*)-*tert*-Butyl 4-fluoro-2-(4-(8-fluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)phenylcarbamate. A solution of the (*R*)-8-fluorochroman-4-amine hydrochloride (104 mg) in DMSO (2 mL) and potassium carbonate (141 mg) were added to a stirred solution of *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)phenylcarbamate (140 mg) in ACN (10 mL). The mixture was stirred for 15 hr at room temperature then partitioned between brine and EtOAc and separated. The aq. layer was washed with additional EtOAc, the combined organics were evaporated and purified via column chromatography, elution with 20-30 % EtOAc/H gave the titled product in 83 % yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.1 (s, 1H), 8.7(m, 1H), 8.2 (br s, 1H), 7.7 (m, 1H), 7.3 (m, 1H), 7.3-6.8 (m, 4H), 6.5 (s, 1H), 5.5 (br s,1H), 4.4 (m 2H), 2.4 (m, 1H), 2.2 (m, 1H), 1.5 (s, 9H); MH^+ = 515, 459 (-*t*Bu).

[00268] (*R*)-*tert*-Butyl 4-fluoro-2-(9-(8-fluorochroman-4-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-ylamino)phenylcarbamate. To a solution of (*R*)-*tert*-butyl 4-fluoro-2-(4-(8-fluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)phenylcarbamate (141 mg) in THF (20 mL) was added a premixed solution of sodium hydrosulfite (0.6 g) and sodium bicarbonate (0.3g) in water (50 mL). MeOH (5 mL) was also added to aid solution of the mixture, which was stirred at room temperature for 30 min, when

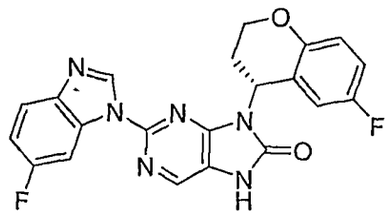
sodium chloride was added to saturate the solution. The resultant mixture was extracted with EtOAc (2x), the combined organics were dried, filtered and evaporated to yield (*R*)-*tert*-butyl 2-(5-amino-4-(8-fluorochroman-4-ylamino)pyrimidin-2-ylamino)-4-fluorophenylcarbamate that was used as such for the next step, MH^+ = 485.

[00269] To a stirred solution of the above material in THF (5 mL) was added CDI (131 mg). After 15 hr brine and EtOAc were added and the mixture was separated. The aq. layer was washed with additional EtOAc and the combined organics were evaporated and purified by column chromatography (eluted 3 % MeOH/DCM) to yield titled product (86 mg, 62 % yield for two steps). ^{1}H-NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 7.9 (s, 1H), 7.4 (dd, 1H), 7.3 (m, 1H), 6.9 (dd, 1H), 6.7-6.5 (m, 3H), 5.7 (dd,1H), 4.6 (m 1H), 4.3(td, 1H), 2.9 (m, 1H), 2.2 (m, 1H), 1.5 (s, 9H); MH^+ = 511, 411 (-BOC), 455 (-*t*Bu).

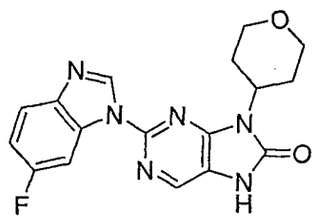
[00270] 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one. A freshly prepared solution of 30 % TFA/DCM (5 mL) was added to (*R*)-*tert*-butyl 4-fluoro-2-(9-(8-fluorochroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-ylamino)phenylcarbamate and the solution was stirred at room temperature for 60 min then the solvents were removed *in vacuo* to yield (*R*)-2-(2-amino-5-fluorophenylamino)-9-(8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one that was used as such MH^+ = 411.

[00271] To the above di-amine was added MeOH (2 mL), trimethylorthoformate (2 mL) and *p*-TsOH (cat). The mixture was stirred at RT for 60 min then the solvents were reduced and the resultant material partitioned between DCM and brine and separated. The crude product was purified via column chromatography (eluted with 4 % MeOH/DCM) to yield the titled compound (46 mg). ^{1}H-NMR (300 MHz, 5%

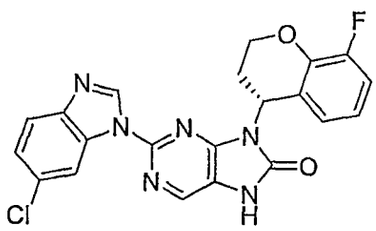
CD_3OD in $CDCl_3$) δ 8.7 (s, 1H), 8.1 (s, 1H), 7.5 (m, 2H), 6.9 (m, 2H), 6.6 (m, 2H), 5.8 (dd, 1H), 4.6 (m 1H), 4.3 (td, 1H), 2.8 (m, 1H), 2.3 (m, 1H); $MH^+ = 421$.



[00272] 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-((R)-6-fluorochroman-4-yl)-7H-purin-8(9H)-one. The title compound was synthesized from (*R*)-6-fluorochroman-4-amine via the procedures described in Example 27. ^1H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.72 (s, 1H), 8.16 (s, 1H), 7.5-7.7 (m, 2H), 6.9-7.0 (m, 2H), 6.8-6.9 (m, 1H), 6.54 (dd, 1H), 5.78 (br t, 1H), 4.4-4.5 (m, 1H), 4.26 (m, 1H), 2.7-2.8 (m, 1H), 2.2-2.3 (m, 1H).

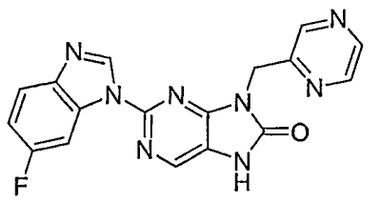


[00273] 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one. The title compound was synthesized from 4-aminotetrahydropyran via the procedures described in Example 27. ^1H NMR (d_6-DMSO) δ 11.65 (s, 1H), 9.13 (s, 1H), 8.34 (s, 1H), 8.28 (m, 1H), 7.82 (m, 1H), 7.25 (td, J = 9.0, 2.4 Hz, 1H), 4.56 (m, 1H), 4.03 (dd, J = 11.1, 3.9 Hz, 2H), 3.50 (t, J = 11.1 Hz, 2H), 2.59 (m, 2H), 1.78 (m, 2H).



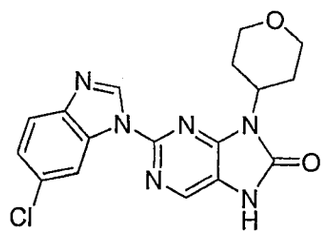
[00274] 2-(6-Chloro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one. The title compound was synthesized from (*R*)-8-fluorochroman-4-amine and 4-chloro-2-nitrobenzenamine via the procedures described in Example 27. ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.7 (s, 1H), 8.2 (s, 1H), 8.1 (s, 1H), 7.6 (d, 1H), 7.2 (dd, 1H), 6.9 (td, 1H), 6.7-6.5 (m, 2H). 5.8 (dd, 1H), 4.6 (m 1H), 4.4 (td, 1H), 2.9 (m, 1H), 2.3 (m, 1H).

[00275] Synthesis of 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-(pyrazin-2-ylmethyl)-7*H*-purin-8(9*H*)-one.



[00276] The title compound was synthesized from pyrazin-2-ylmethanamine via the procedure described in Example 27. ^{1}H-NMR (300 MHz, $CDCl_3$ + 5% CD_3OD) δ 8.9 (br, 1H), 8.7 (s, 1H), 8.5 (s, 1H), 8.5 (s, 1H) 8.2 (s, 1H), 8.2(dd, 1H), 7.7 (dd, 1H), 7.0 (td, 1H), 5.3 (s, 2H).

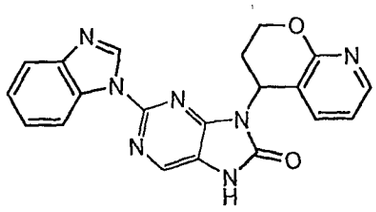
[00277] Synthesis of 2-(6-Chloro-1H-benzo[d]imidazol-1-yl)-9-(tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one.



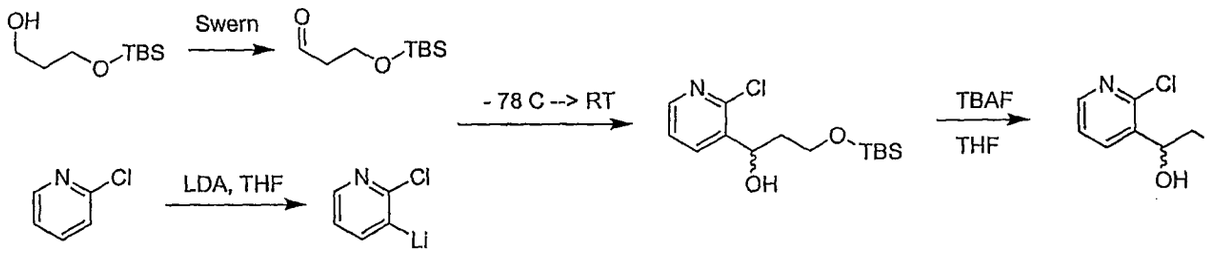
[00278] The title compound was synthesized from 4-aminotetrahydropyran and 4-chloro-2-nitrobenzenamine via the procedures described in Example 27 ^{1}H NMR

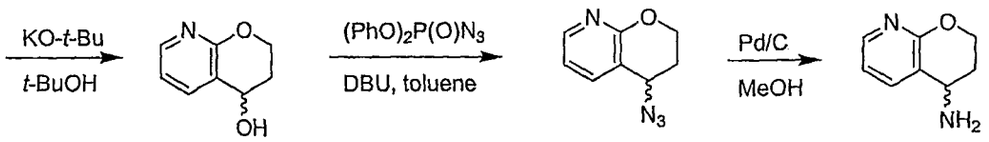
(CD_3OD + $CHCl_3$) δ9.15 (s, 1H), 8.67 (d, 1H), 8.27 (s, 1H), 7.70 (d, 1H), 7.37 (dd, 1H), 4.64 (m, 1H), 4.18 (m, 2H), 3.61 (m, 2H), 2.81 (m, 2H), 1.85 (m, 2H); MS (MH^+) 371.1.

[00279] Procedure for the synthesis of 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-yl)-7*H*-purin-8(9*H*)-one.



[00280] Synthesis of 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-amine





[00281] 3-(*tert*-Butyldimethylsilyloxy)-1-(2-chloropyridin-3-yl)propan-1-ol. (Prepared similarly to literature procedure, Murtiashaw, C. W., *et.al. J. Org. Chem.*, 1992, *57*, 1930-1933). A solution of 3-(*tert*-butyldimethylsilyloxy)propanal (2.3g, prepared from 3-(*tert*-butyldimethylsilyloxy)propan-1-ol via Swern oxidation as per

Li, X.; Lantrip, D.; Fuchs, P. L. *J. Am. Chem. Soc.*, 2003, *125*, 14262-14263, Supporting information) in THF (10 mL) was slowly added via double ended needle to a solution of 2-chloro-3-lithiopyridine (prepared in turn from freshly prepared LDA (11.4 mM) and 2-chloropyridine (11.4 mM) (as per Gribble, G. W.; Saulnier, M. G. *Tet. Lett.* 1980, *21*, 4137-4140) in THF (25 mL) at -78 °C. The resulting mixture was allowed to slowly warm to RT over 15 hr, quenched via the addition of sat. NH_4Cl (2 mL) and solvents reduced *in vacuo*. The resultant slurry was taken up in EtOAc, washed with brine, and purified via column chromatography (eluted with 15, 20 and 25 % EtOAc/Hex) to yield the titled product (1.0 g), NMR $CDCl_3$ ^1H δ 8.3 (dd, 1H), 8.0 (dd, 1H), 7.3 (dd, 1H), 5.2 (d, 1H), 4.5 (m, 1H), 4.0-3.8 (m, 2H), 2.1 (m, 1H), 1.8 (m, 1H) 0.9 (s, 9H), 0.1 (s, 6H); MH^+ = 302/304.

[00282] 1-(2-Chloropyridin-3-yl)propane-1,3-diol. A solution of tetrabutylammonium fluoride in THF (1M, 3.3mL) was added to a solution of 3-(*tert*-butyldimethylsilyloxy)-1-(2-chloropyridin-3-yl)propan-1-ol in THF (5 mL) and stirred for 60 min, then silica gel was added and the solvent were removed under reduced pressure. The entire flask contents were added to a column, that was prepared and eluted with 75 % ETOAC/Hex, to yield that titled product (0.49 g), NMR CD_3OD ^1H δ 8.3 (dd, 1H), 8.0 (dd, 1H), 7.4 (dd, 1H), 5.1 (dd, 1H), 3.8 (m, 2H), 2.0 (m, 1H), 1.8 (m, 1H); MH^+ = 188/190.

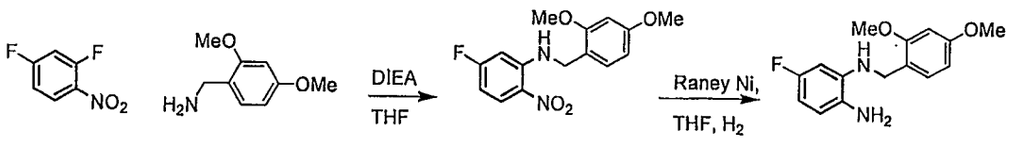
[00283] 3,4-Dihydro-2*H*-pyrano[2,3-b]pyridin-4-ol. Potassium *tert*-butoxide (0.88 g) was added to a solution of 1-(2-chloropyridin-3-yl)propane-1,3-diol (0.49g) in *tert*-butanol and the solution was heated at reflux for 3 hr, allowed to cool to RT, quenched via the addition al of sat. NH_4Cl (2 mL), solvents reduced then silica gel added and remaining solvents removed *in vacuo*. The material was added to a silica gel column that was eluted with EtOAc and 1% MeOH/EtOAc to yield the titled product (0.35 g) NMR $CDCl_3$ ^1H δ 8.1 (dd, 1H), 7.7 (dd, 1H), 6.9 (dd, 1H), 4.9 (dd, 1H), 4.5 (m, 2H), 2.1 (m, 2H); MH^+ = 152.

[00284] 4-Azido-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine. (Prep ref: Phompson, A. S. *et.al. J. Org. Chem.*, 1993, *58*, 5886-5888). Diphenyl phosphoryl azide (0.81 mL) was added to a suspension of 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-ol (0.37 g) in dry toluene (10 mL) then the mixture was cooled to 0°C under an Ar atmosphere. Neat DBU (0.56 mL) was added and the resultant biphasic mixture was stirred at 0°C for 2 hr and then at RT for 15 hr. The biphasic solution was diluted with sat. $NaHCO_3$ and extracted with DCM (2 x). The combined organics were concentrated and purified by silica gel chromatography using 10, 25 and 50 % EtOAc/Hex elutants to afford the titled product (0.31 g) NMR $CDCl_3$ ^1H δ 8.2 (dd, 1H), 7.6 (dd, 1H), 7.0 (dd, 1H), 4.7 (dd, 1H), 4.4 (m, 2H), 2.2 (m, 1H), 2.1 (m, 1H); $MH^+ = 177$.

[00285] 3,4-Dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-amine. A catalytic amount of Pd/C (9 mg) was added to a solution of 4-azido-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (88 mg) in MeOH (5 mL). The flask closed with a septum, evacuated under house vacuum and hydrogen added via balloon. The resulting suspension was stirred at RT for 60 min, when the H_2 balloon was removed, the mixture evacuated and filtered through a plug of celite, that was thoroughly rinsed with MeOH. Removal of the solvents gave the titled compound (73 mg), NMR $CDCl_3$ ^1H δ 8.1 (dd, 1H), 7.7 (dd, 1H), 6.9 (dd, 1H), 4.5-4.3 (m, 2H), 4.1 (dd, 1H), 2.2 (m, 1H), 1.9 (m, 1H), 1.6 (br s, 2H); $MH^+ = 151$.

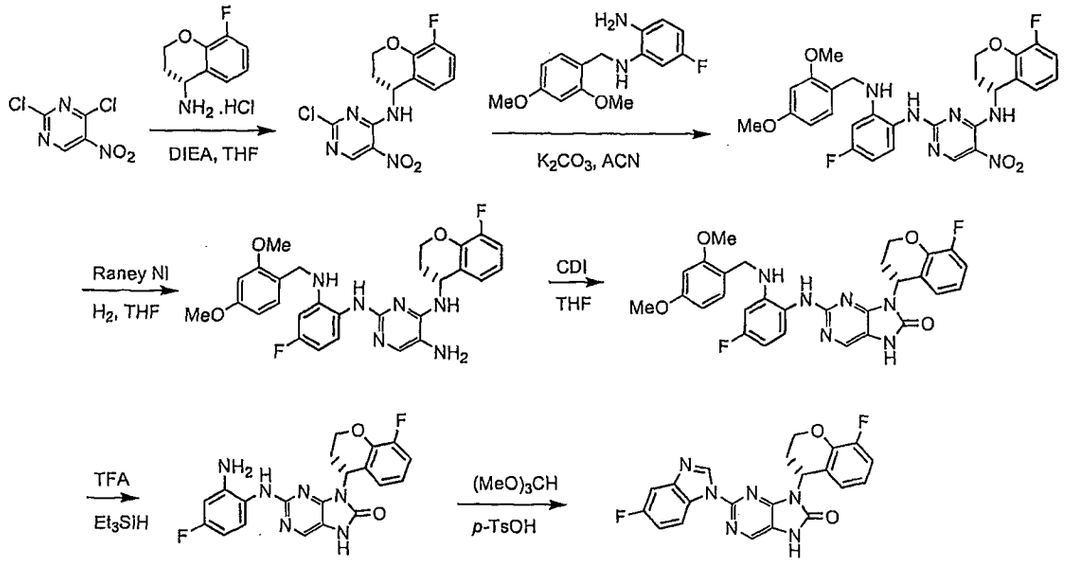
[00286] 2-(1*H*-Benzo[*d*]imidazol-1-yl)-9-(3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-yl)-7*H*-purin-8(9*H*)-one. The titled compound was prepared in the same manner described in Example 19 from 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-amine. ^1H NMR ($CDCl_3$ + 5% CD_3OD) δ 8.8 (s, 1H), 8.2 (s, 1H), 8.1 (m, 1H), 7.7 (m, 2H), 7.3 (m, 2H), 6.8 (dd, 2H), 5.9 (dd, 1H), 4.7 (m 1H), 4.5 (td, 1H), 2.9 (m, 1H), 2.3 (m, 1H); $MH^+ = 386$.

[00287] Example 28: Synthesis of 2-(5-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one:



[00288] *N*-(2,4-Dimethoxybenzyl)-5-fluoro-2-nitrobenzenamine. A solution of 2,4-difluoro-1-nitrobenzene (1.1 mL), 2,4-dimethoxy benzylamine (1.5 mL) and DIEA (5.2 mL), in THF (40 mL) was heated at 60 °C for 60 min, allowed to cool to RT, partitioned between EtOAc and H_20, separated, dried ($MgSO_4$), filtered and evaporated to yield the titled product as a yellow solid (3.14 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.5 (br s, 1H), 7.2 (dd, 1H), 7.2 (d, 1H), 6.6-6.4 (m, 3H), 6.3 (m, 1H), 4.3(d, 2H), 3.9 (s, 3H), 3.8 (s, 3H).

[00289] N^1-(2,4-Dimethoxybenzyl)-5-fluorobenzene-1,2-diamine. Under a flush of Ar, a catalytic amount of a Raney Ni solution in water was added to a solution of *N*-(2,4-dimethoxybenzyl)-5-fluoro-2-nitrobenzenamine (0.5 g) in THF (20 mL). The flask was closed with a septum, evacuated under house vacuum and hydrogen added via balloon. The resulting suspension was stirred at RT for 16 hr, when the H_2 balloon was removed, mixture evacuated and filtered through a plug of celite, that was thoroughly rinsed with THF and MeOH, to yield the titled diamine that was used as such.



[00290] (*R*)-2-Chloro-*N*-(8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine. A solution of (*R*)-8-fluorochroman-4-amine hydrochloride (1.02 g) and DIEA (2.6 mL) in DCM (10 mL) was slowly added to a solution of 2,4-dichloro-5-nitropyrimidine (0.97 g) THF (25 mL) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C then allowed to warm to RT overnight. The reaction was quenched with the addition of sat. NH_4Cl (1 mL), the solvent volume was reduced *in vacuo*, and the resulting mixture partition between EtOAc and water then separated. The crude material was purified via column chromatography, elution with 30 % EtOAc/Hex gave the titled product (1.43 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.1 (s, 1H), 8.6 (br d, 1H), 7.1-6.8 (m, 3H), 5.6 (dd,1H), 4.4 (m 1H), 4.3(m, 1H), 2.4 (m, 1H), 2.2 (m, 1H).

[00291] (*R*)-N^2-(2-(2,4-Dimethoxybenzylamino)-4-fluorophenyl)-N^4-(8-fluorochroman-4-yl)-5-nitropyrimidine-2,4-diamine. A mixture of (*R*)-2-chloro-*N*-(8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine (32 mg), N^1-(2,4-dimethoxybenzyl)-5-fluorobenzene-1,2-diamine (28 mg)and KCO_3 (41 mg) in ACN was heated at 65 °C for 3 hr, cooled to RT, diluted with brine and extracted with EtOAc (2x). The combined organics were evaporated, and purified by column chromatography (eluted

with 30 % EtOAc/Hex) to yield the titled product (21 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.6 (br d, 1H), 7.2-6.8 (m, 6H), 6.5-6.3 (m,4H), 4.4-4.2 (m, 4H), 3.8 (s, 6H), 2.3-2.2 (m, 2H).

[00292] (*R*)-2-(2-(2,4-Dimethoxybenzylamino)-4-fluorophenylamino)-9-(8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one. Under an Ar atmosphere, a catalytic amount of a Raney Ni solution in water was added to a solution of (*R*)-N^2-(2-(2,4-dimethoxybenzylamino)-4-fluorophenyl)-N^4-(8-fluorochroman-4-yl)-5-nitropyrimidine-2,4-diamine (21 mg) in THF. The flask was closed with a septum, evacuated under house vacuum and hydrogen added via balloon. The resulting suspension was stirred at RT for 2 hr, when the H_2 balloon was removed, the mixture evacuated and filtered through a plug of celite, that was thoroughly rinsed with THF and MeOH, to yield (*R*)-N^2-(2-(2,4-dimethoxybenzylamino)-4-fluorophenyl)-N^4-(8-fluorochroman-4-yl)pyrimidine-2,4,5-triamine that was used directly.

[00293] To a stirred solution of the above material in THF (5 mL) was added CDI (12 mg). After 18 hr brine and EtOAc were added and the mixture was separated. The organic layer was evaporated and purified by column chromatography (eluted 4 % MeOH/DCM) to yield titled product (14 mg). ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 7.8 (s, 1H), 7.3 (s, 1H), 7.1 (d, 1H), 6.9 (m, 2H), 6.7-6.2 (m, 6H), 5.7 (dd, 1H), 4.5 (m 1H), 4.2 (m, 1H), 4.1 (s, 2H), 3.8 (s, 3H), 3.7 (s, 3H), 2.8 (m, 1H), 2.2 (m, 1H).

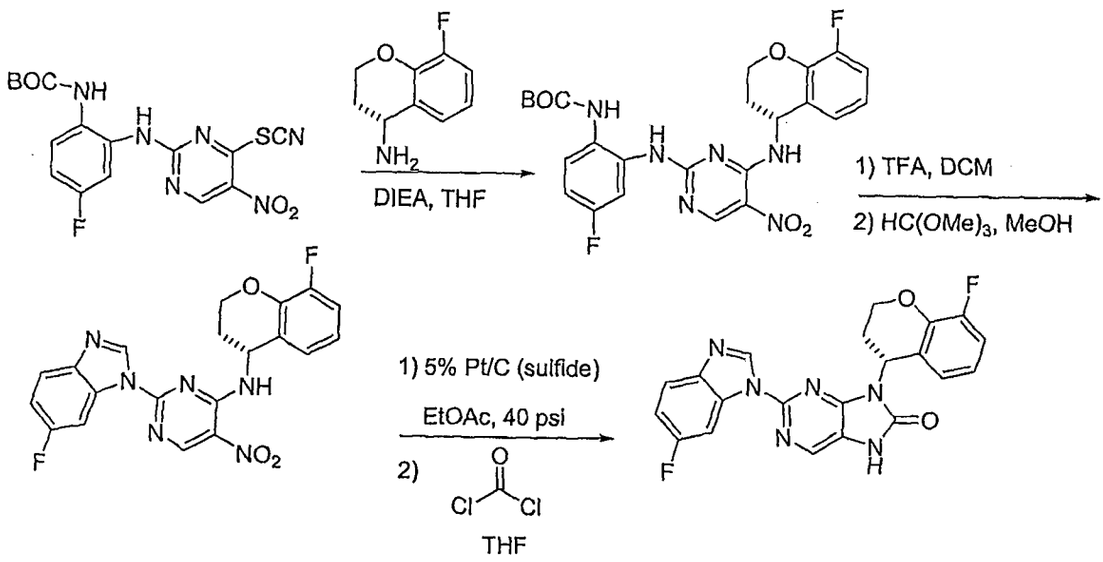
[00294] 2-(5-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one.

[00295] A mixture of (*R*)-2-(2-(2,4-dimethoxybenzylamino)-4-fluorophenylamino)-9-(8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one (14 mg) and TFA (1 mL) was stirred for 60 min when triethyl silane (0.5 mL) was added. The resulting solution was stirred at RT for 16 hr, then the solvents were reduced *in vacuo* to yield (*R*)-2-(2-amino-4-

fluorophenylamino)-9-(8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one that was used as such.

[00296] A catalytic amount of *p*-TsOH was added to a solution of the above amine in trimethylorthoformate (2 mL). The mixture was stirred at RT for 15 hr then the solvents were reduced and the resultant material partitioned between DCM and brine and separated.. The crude product was purified via column chromatography (eluted with 5 % MeOH/DCM) to yield the titled compound (9 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.9 (s, 1H), 8.3 (s, 1H), 7.8 (dd, 1H), 7.4 (d, 1H), 7.1 (m, 2H), 6.8 (m, 2H), 5.9 (dd, 1H), 4.7 (m 1H), 4.4 (td, 1H), 2.9 (m, 1H), 2.4 (m, 1H).

[00297] Synthesis of 2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one.



[00298] (*R*)-*tert*-Butyl 4-fluoro-2-(4-(8-fluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)phenylcarbamate. *tert*-Butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)phenylcarbamate (2.0 g) was added to a solution of

(*R*)-8-fluorochroman-4-amine hydrochloride (1.1 gram) and *N, N*-diisopropylethylamine (2.2 mL) in THF (anhydrous, 50 mL). The mixture was stirred for 6 hr at room temperature then partitioned between water and EtOAc and separated. The aq. layer was washed with additional EtOAc and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give the title product in 94% yield. $MH^+ = 515$, 459 (-*t*Bu).

[00299] 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-N-((*R*)-8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine. A freshly prepared solution of 30% TFA/DCM (100 mL) was added to (*R*)-*tert*-butyl 4-fluoro-2-(4-(8-fluorochroman-4-ylamino)-5-nitropyrimidin-2-ylamino)phenylcarbamate and the solution was stirred at room temperature for 60 min. The solvents were removed *in vacuo* to yield (*R*)-N2-(2-amino-5-fluorophenyl)-N4-(8-fluorochroman-4-yl)-5-nitropyrimidine-2,4-diamine that was carried on without further purification. $MH^+ = 415$.

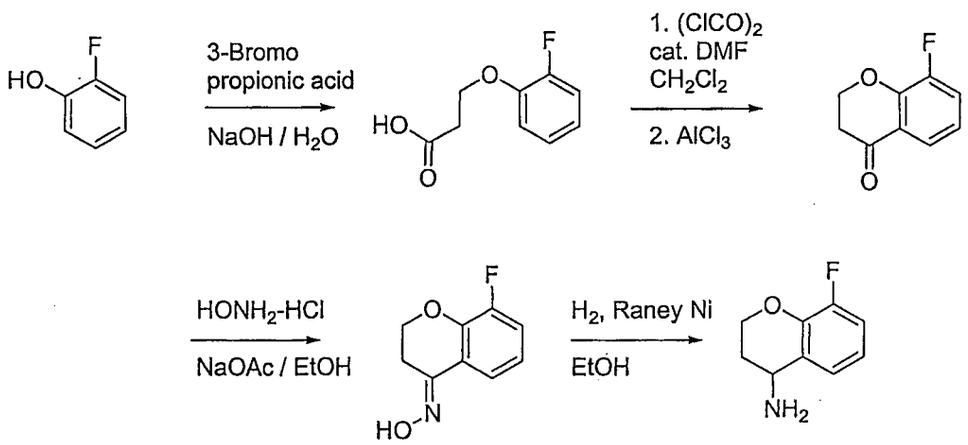
[00300] To the above diamine was added MeOH (50 mL) and trimethylorthoformate (50 mL). The mixture was stirred for 30 minutes at room temperature, and the solvents were removed *in vacuo* to yield crude 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-N-((R)-8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine in 94% yield (2 steps). $MH^+ = 425$.

[00301] 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-yl)-9-((*R*)-8-fluorochroman-4-yl)-7*H*-purin-8(9*H*)-one. To a solution of the 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-N-((R)-8-fluorochroman-4-yl)-5-nitropyrimidin-4-amine in EtOAc (20 mL) was added 5 mol% of Platinum, 5% on activated carbon power, sulfide, 0.5% S (as sulfide) (45.6 mg). The mixture was sparged with argon, transferred to the Parr hydrogenation apparatus, then subjected to a purge/fill sequence with hydrogen (repeated 5X). The mixture was hydrogenated for 18hr at 40 psi. Filtration through a pad of Celite and concentration of the filtrate gave crude 2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)N^4-((*R*)-

8-fluorochroman-4-yl)pyrimidine-4,5-diamine that was carried on without further purification. $MH^+ = 425$.

[00302] To a solution of the above diamine in THF (50 mL) was added dropwise 20% phosgene solution in toluene at room temperature. A light brown precipitate formed immediately. Stirring was maintained for an additional 30 min at room temperature and the solvents were removed *in vacuo* to yield the titled compund. The crude product was crystallized from hot EtOAc to yield 1.10 g (53%, 2 steps) of the title compound as off white solid. Treatment with 5 mL methanol and 5 mL of HCl (conc. aq) gave 1.25 g of the hydrochloride salt as off white solid. ^{1}H-NMR (300 MHz, CD_3OD) δ 10.0 (s, 1H), 8.4 (s, 1H), 7.9-7.8 (m, 2H), 7.5 (td, 1H), 7.0-6.9 (m, 1H), 6.7-6.6 (m, 2H), 5.9 (dd, 1H), 4.6 (dt, 1H), 4.4 (td, 1H), 2.9-2.8 (m, 1H), 2.4-2.3 (m, 1H); $MH^+ = 421$.

[00303] Example 29. Synthesis and Resolution of 8-Fluorochroman-4-amine:

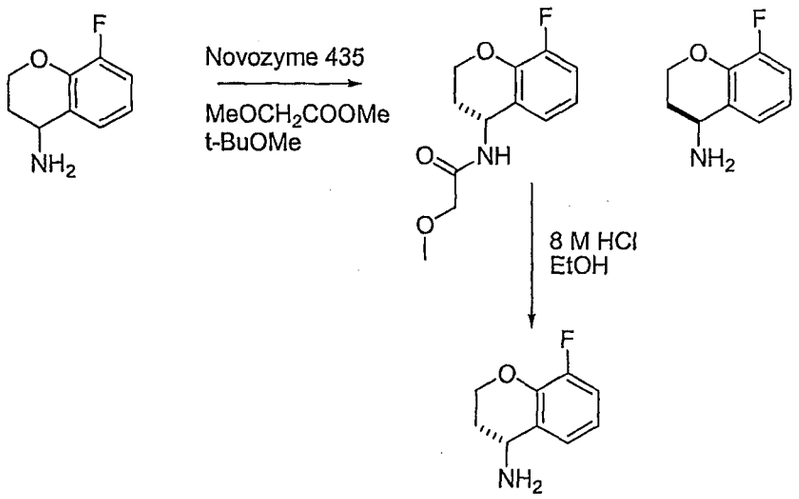


[00304] 3-(2-Fluorophenoxy)propanoic acid. A mixture of 2-fluorophenol (15 g), 3-bromopropanoic acid (20 g) and NaOH (11 g) was refluxed in 50mL of water. The solution was cooled to room temperature and acidified to pH 2 with 3 M HCl. The resulting precipitate was isolated by filtration to yield 9.27 g of title compound as a

white solid. The filtrate was extracted 3 times with EtOAc to yield 2.5g of less pure compound.

[00305] 8-Fluorochroman-4-one. Oxalyl chloride (8.79 mL) and 1 drop of DMF were added to an ice cold solution of 3-(2-fluorophenoxy)propanoic acid (9.27 g) in DCM (50 mL). The solution was stirred at 0 °C for 2 hours, then aluminum chloride (7.39g, 55.42mM) was added and the solution was stirred for 16 hours at room temperature. The mixture was poured onto ice water, and extracted three times with DCM. The combined organics were washed with 0.5M NaOH and brine, then dried, evaporated, and purified by column chromatography (eluting with 20% EtOAc/Hex) to give of the title compound (8.20g, 98%).

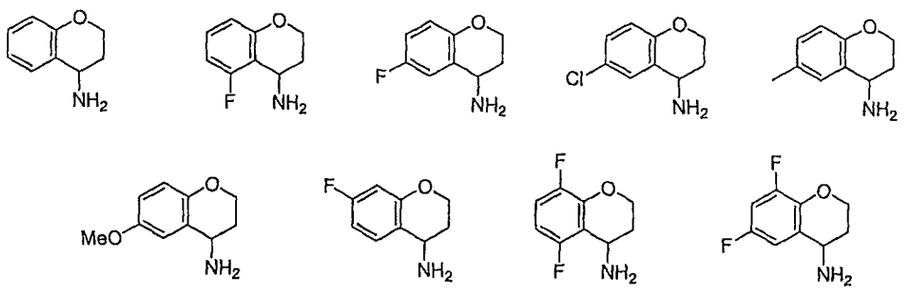
[00306] 8-Fluorochroman-4-amine. A round bottom flask was charged with 8-fluorochroman-4-one (8.2g), hydroxylamine hydrochloride (3.78g) and sodium acetate (4.46g). A reflux condenser was added, the flask was purged with argon, dry EtOH (20 mL) was added, and the mixture was stirred at reflux for 18 hours. The solution was cooled to room temperature, diluted with EtOAc, and washed with water. The organic phase was dried, and evaporated to give the intermediate 8-fluorochroman-4-one oxime, which was reduced with Raney Nickel in EtOH at 50 PSI to yield the titled amine (4.69g, 57%).



[00307] Resolution of 8-fluorochroman-4-amine. (Procedure based on US published application 2004/0157739). A mixture of 8-fluorochroman-4-amine (3.40 g), methyl 2-methoxyacetate (2.44 g) and Novozyme 435 (Aldrich, 0.68 g) in anhydrous *tert*-butyl methyl ether (75mL) was heated at reflux under argon for 2 hours (at which time the ratio of acylated to unacylated product was 1:1 by HPLC). The solid that formed upon cooling was collected via filtration and dissolved in EtOAc. The mixture was filtered to remove the biocatalyst and washed once with 0.5M HCl to remove any lingering (S)-amine. The solvent was evaporated and the product was recrystallized from *tert*-butyl methyl ether to yield (R)-N-(8-fluorochroman-4-yl)-2-methoxyacetamide (0.78 g). The reaction solvent and recrystallization mother liquor was washed 3 times with 0.5 M HCl and concentrated to yield additional (R)-N-(8-fluorochroman-4-yl)-2-methoxyacetamide (0.83 g). The combined acidic aqueous layers were made basic by NaOH and extracted with DCM to yield (*S*)-8-fluorochroman-4-amine (1.6g). A solution of (*R*)-N-(8-fluorochroman-4-yl)-2-methoxyacetamide (0.78g) in 8M HCl in EtOH (50mL) was heated at reflux for 4 hours. The solvents were removed from the cooled reaction mixture, the resulting solid was taken up in 50 mL of 0.5M NaOH, salted out with $NaCl_{(s)}$, and extracted 4 times with DCM to yield (R)-8-fluorochroman-4-amine (0.48 g (87%)). The % ee was

checked via chiral HPLC: Chiralcel OD-H (0.46 x 25 cm analytical column, Daicel Chemical Industries) method: isocratic 5 % (0.05% TFA/EtOH) 95 % (0.05 % TFA/Hex), Rt = 7.2 min (*S*)-enantiomer, Rt = 9.2 min (*R*)-enantiomer.

[00308] Example 30. Chroman-4-amine, 5-fluorochroman-4-amine, 6-fluorochroman-4-amine, 6-chlorochroman-4-amine, 6-methylchroman-4-amine, 6-methoxychroman-4-amine, 7-fluorochroman-4-amine, 5,8-difluorochroman-4-amine, and 6,8-difluorochroman-4-amine.



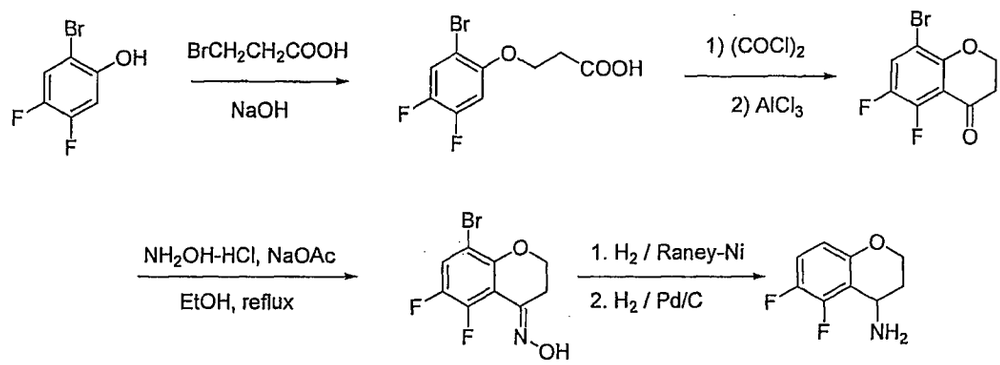
[00309] These amines were prepared via procedures described in Example 29 for the synthesis of 8-fluorochroman-4-amine. The corresponding chroman-4-ones were commercially available as advanced intermediates for the synthesis of chroman-4-amine, 6-fluorochroman-4-amine, 6-chlorochroman-4-amine, 6-methylchroman-4-amine, and 6-methoxychroman-4-amine. For the synthesis of 5-fluorochroman-4-amine, the intermediate 5-fluorochroman-4-one was obtained using procedures from GB 2355264, which also provided 7-fluorochroman-4-one. 7-Fluorochroman-4-one could be used in the synthesis of 7-fluorochroman-4-amine. Chroman-4-amine, 5-fluorochroman-4-amine, 6-fluorochroman-4-amine, 7-fluorochroman-4-amine, 5,8-difluorochroman-4-amine, and 6,8-difluorochroman-4-amine were resolved via the procedure described in Example 29 for the resolution of 8-fluorochroman-4-amine.

[00310] Example 31. 1-Methyl-4,5,6,7-tetrahydro-1H-indol-4-amine.



[00311] The title compound was obtained from 1-methyl-6,7-dihydro-1H-indol-4(5H)-one (Heterocycles (1984), 22, 2313) via the procedure described in Example 29 that were used to obtain 8-fluorochroman-4-amine from 8-fluorochroman-4-one.

[00312] Example 32. Synthesis of 5,6-Difluorochroman-4-amine:



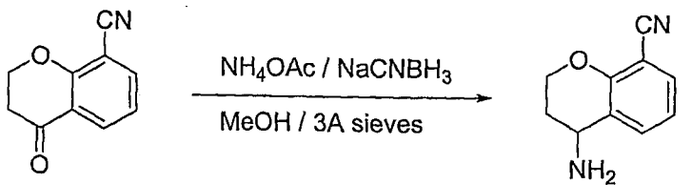
[00313] 3-(2-Bromo-4,5-difluorophenoxy)propanoic acid. A solution of 1.68 g of NaOH (42 mmol) in 5 mL of water was added slowly to the suspension of 2.29 mL (20 mmol) 2-bromo-4,5-difluorophenol and 3.07 g (20 mmol) 3-bromopropionic acid. The mixture was heated at 100 °C in an oil bath for 5 hours, and then allowed to cool to room temperature. Water was added to completely dissolve any solid material and the reaction mixture was made acidic with concentrated HCl. The product was extracted into ether (3 times), and the combined organic layers was dried over Na_2SO_4 and evaporated to give 3.7 g (66%) of the title compound as a light brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.4 (t, 1H), 6.8 (q, 1H), 4.3 (t, 2H), 2.9 (t, 2H).

[00314] 8-Bromo-5,6-difluoro-2,3-dihydrochromen-4-one. Oxalyl chloride (1.7 mL, 20 mmol) was added to the solution of 2.8 g (10 mmol) of 3-(2-bromo-4,5-difluorophenoxy)-propanoic acid in 40 mL of anhydrous DCM followed by a drop of DMF. After 1.5 hours, a drying tube was attached and the solution was cooled in an ice-water bath. $AlCl_3$ (1.5 g, 11 mmol) was added and the dark red solution was allowed to slowly reach room temperature while being stirred for 16 hours. The mixture was poured into ice and the organic layer was separated. The aqueous layer was extracted with DCM twice. The combined organic layers were washed with 0.5 N NaOH and brine, then dried over Na_2SO_4 and concentrated. Column chromatography of this residue with hexane and EtOAc provided 1.9 g of the title compound as an off-white solid (73%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.6 (t, 1H), 4.65 (t, 2H), 2.85 (t, 2H).

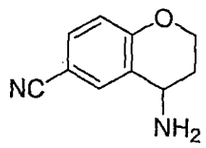
[00315] 8-Bromo-5,6-difluoro-2,3-dihydrochromen-4-one oxime. To a solution of 8-bromo-5,6-difluoro-2,3-dihydrochromen-4-one (7.2 mmol) in 40 mL of ethanol was added hydroxylamine hydrochloride (0.55 g, 7.9 mmol) and sodium acetate (0.65 g, 7.9 mmol). This mixture heated at reflux for 20 hrs. The mixture was cooled, diluted with EtOAc, washed with water and brine, and then dried over Na_2SO_4. Concentration of the solvent provided the title compound as a white solid (1.9 g). ^1H NMR (300 MHz, 10% CD_3OD in $CDCl_3$): δ 7.3 (t, 1H), 4.2 (t, 2H), 2.9 (t, 2H).

[00316] 5,6-Difluoro-3,4-dihydro-2H-chromen-4-amine. Raney-Ni (5 mL slurry in water) was added to a solution of 8-bromo-5,6-difluoro-2,3-dihydrochromen-4-one oxime (1.9 g) in 200 mL MeOH. The mixture was hydrogenated at 50 psi for 24 hrs to provide 8-bromo-5,6-difluoro-3,4-dihydro-2H-chromen-4-amine. Pd/C (0.3 g) was added to the mixture and hydrogenation was resumed at 50 psi for 4 hours. The title compound was obtained after filtration and concentration *in vacuo*. ^1H NMR (300 MHz, 10% CD_3OD in $CDCl_3$): δ 7.15 (q, 1H), 6.6 (m, 1H), 4.6 (bm, 1H), 4.25 (bm, 2H), 2.2-2.4 (m, 2H).

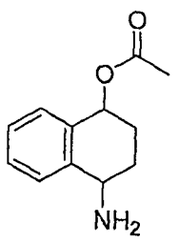
[00317] Example 33. Synthesis of 4-Amino-3,4-dihydro-2H-chromene-8-carbonitrile:



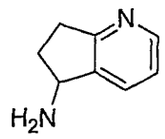
[00318] 4-Amino-3,4-dihydro-2H-chromene-8-carbonitrile. A mixture of 260 mg of 4-oxo-3,4-dihydro-2H-chromene-8-carbonitrile (made from 2-hydroxybenzonitrile via the procedure described in Example 29), ammonium acetate (1.2 g), and 3A molecular sieves (1.5 g) in 10 mL of methanol was stirred for 5 days. The mixture was filtered through celite and the filtrate concentrated *in vacuo*. The crude residue was treated with 100 mL of 1 M HCl and extracted with ethyl ether (3 X 100 mL). The aqueous layer was made basic to pH 10 with saturated NaOH and extracted with DCM (3 X 100 mL). The combined DCM layers were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to provide 150 mg of the title compound.



[00319] 4-Amino-3,4-dihydro-2H-chromene-6-carbonitrile. The title compound was made from 6-cyano-4-chromanone (Syntech) via the same procedure that was described in Example 33.

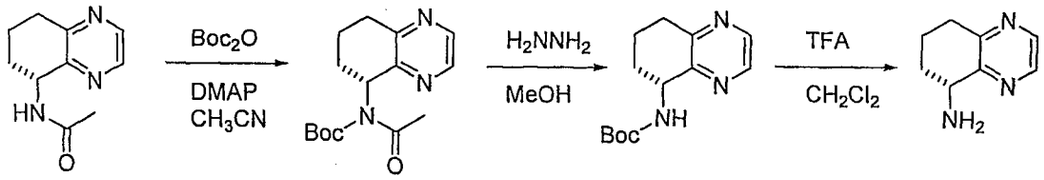


[00320] 4-Amino-1,2,3,4-tetrahydronaphthalen-1-yl acetate. The title compound was made from 4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (Tetrahedron: Asymmetry 2001, 12, 2283) via the same procedure that was described in Example 33.



[00321] 6,7-Dihydro-5H-cyclopenta[b]pyridin-5-amine. The title compound was made as described in WO 03/045924.

[00322] Example 34. Synthesis of (R)-5,6,7,8-Tetrahydroquinoxalin-5-amine:



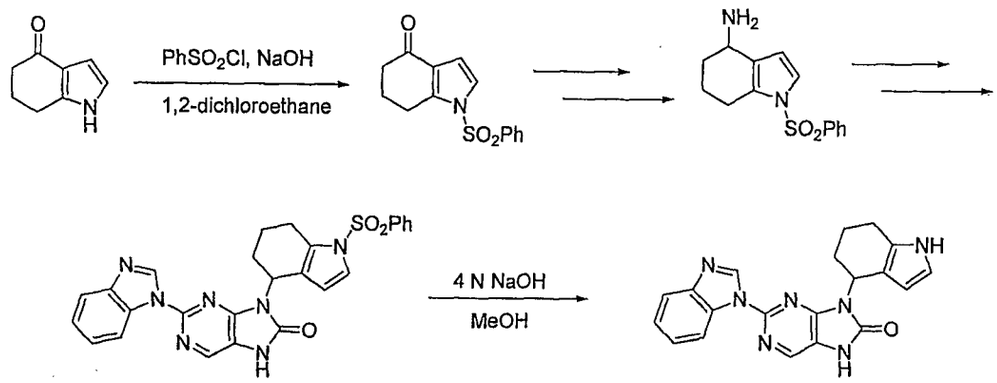
[00323] (R)-tert-Butyl acetyl(5,6,7,8-tetrahydroquinoxalin-5-yl)carbamate. A solution containing 483 mg of (R)-N-(5,6,7,8-tetrahydroquinoxalin-5-yl)acetamide (J. Org. Chem. (2003), 68, 3546) in acetonitrile (20 mL) was treated with Boc_2O (3 g) and DMAP (5 mg). The mixture was heated at 60 °C for 1.5 h and then concentrated *in vacuo*. Column chromatography (50% EtOAc / hexanes) provided 293 mg of the title compound.

[00324] (R)-tert-Butyl 5,6,7,8-tetrahydroquinoxalin-5-ylcarbamate. A solution of (R)-tert-butyl acetyl(5,6,7,8-tetrahydroquinoxalin-5-yl)carbamate (293 mg) in methanol (10 mL) was treated with hydrazine hydrate (0.5 mL) for 1.5 h. The mixture was diluted with EtOAc and washed twice with saturated aqueous sodium chloride. The organic layer was separated, dried with sodium sulfate, and concentrated *in vacuo* to provide 238 mg of the title compound.

[00325] 2,3-dihydrobenzofuran-3-amine. To the solution of benzofuran-3(2H)-one oxime (1.0 g, obtained from commercially available benzofuran-3(2H)-one via the procedure outlined for the synthesis of 4-fluorobenzofuran-3(2H)-one oxime from 4-fluorobenzofuran-3(2H)-one) in 50 mL MeOH, 10% Palladium on active carbon (0.1 g) was added. The mixture was evacuated then filled with H_2 three times. Finally the oxime was reduced under a H_2 balloon for 24 hours. The mixture was filtered through a pad of celite, and the cake was washed with MeOH twice. After removing the solvents under vacuum, 0.99 g brown-yellow residue was obtained as the desired amine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 1H), 7.19 (t, 1H), 6.94 (t, 1H), 6.82 (d, 1H), 4.5-4.7 (m, 1H), 4.64 (s, 1H), 4.1-4.2 (m, 1H).

[00326] (R)-5,6,7,8-Tetrahydroquinoxalin-5-amine. A solution of (R)-tert-butyl 5,6,7,8-tetrahydroquinoxalin-5-ylcarbamate (238 mg) in 10 ml of 1:1 TFA / DCM was stirred for 30 minutes. The mixture was concentrated *in vacuo* to provide the title compound as the TFA salt.

[00327] Example 35. Synthesis of 2-(1H-Benzo[d]imidazol-1-yl)-9-(4,5,6,7-tetrahydro-1H-indol-4-yl)-7H-purin-8(9H)-one:



[00328] 1-(Phenylsulfonyl)-4-oxo-4,5,6,7-tetrahydroindole. To a suspension of NaOH (4.44 g) in 1,2-dichloroethane (250 mL) was added 4-oxo-4,5,6,7-tetrahydroindole (5.0 g). The mixture was then cooled to 0 °C and stirred for 30 min,

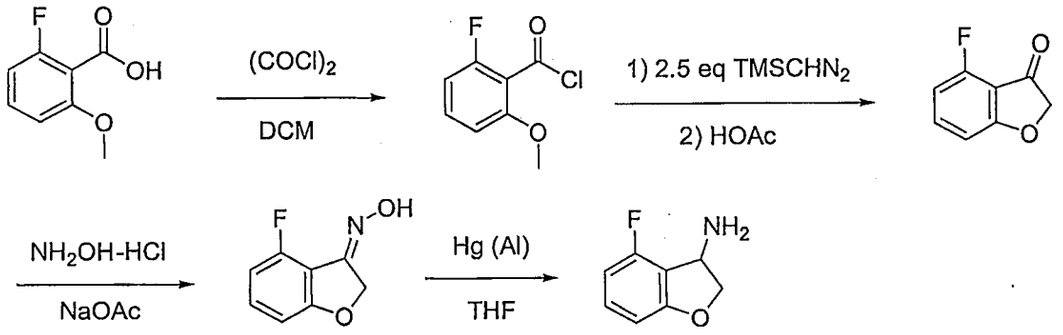
following which a solution of phenylsulfonyl chloride (5.7 mL) in 1,2-dichloroethane (50 mL) was added dropwise over a period of 30 min. After 30 min of stirring, the reaction mixture was allowed to come to room temperature and stirred overnight. The reaction was quenched by pouring onto distilled water (100 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extract was washed with distilled water to neutrality, dried over $MgSO_4$, and concentrated in vacuo to afford 7.0 g of the title compound.

[00329] 1-(Phenylsulfonyl)-4,5,6,7-tetrahydro-1H-indol-4-amine. The title compound was obtained from 1-(phenylsulfonyl)-4-oxo-4,5,6,7-tetrahydroindole via the procedure described in Example 29 that was used to obtain 8-fluorochroman-4-amine from 8-fluorochroman-4-one.

[00330] 2-(1H-Benzo[d]imidazol-1-yl)-9-(1-(phenylsulfonyl)-4,5,6,7-tetrahydro-1H-indol-4-yl)-7H-purin-8(9H)-one. The title compound was obtained from 1-(phenylsulfonyl)-4,5,6,7-tetrahydro-1H-indol-4-amine via the procedures described in Example 24.

[00331] 2-(1*H*-benzo[*d*]imidazol-1-yl)-9-(4,5,6,7-tetrahydro-1*H*-indol-4-yl)-7*H*-purin-8(9*H*)-one. To a solution of 2-(1*H*-benzo[*d*]imidazol-1-yl)-9-(1-(phenylsulfonyl)-4,5,6,7-tetrahydro-1*H*-indol-4-yl)-7*H*-purin-8(9*H*)-one (50 mg) in MeOH (1 mL) was added 4 N NaOH (1 mL), and the mixture was refluxed overnight and cooled. Volatiles were removed under reduced pressure, and the resultant neutralized with 4 N HCl. The white precipitate was filtered, washed with a small amount of water, and dried in vacuo to afford 36 mg of the title compound. ^{1}H NMR (d_6-DMSO) δ 11.6 (s, 1H), 10.7 (s, 1H), 8.86 (s, 1H), 8.27 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.33 (m, 2H), 6.53 (t, J = 2.4 Hz, 1H), 5.64 (t, J = 2.4 Hz, 1H), 5.54 (m, 1H), 2.72 (m, 2H), 2.30 (m, 1H), 2.07 (m, 2H), 1.84 (m, 1H).

[00332] Examples 36 and 37 (Dihydrobenzofurans): 2-(1H-benzo[d]imidazol-1-yl)-9-(2,3-dihydrobenzofuran-3-yl)-7H-purin-8(9H)-one and 2-(1H-benzo[d]imidazol-1-yl)-9-(4-fluoro-2,3-dihydrobenzofuran-3-yl)-7H-purin-8(9H)-one



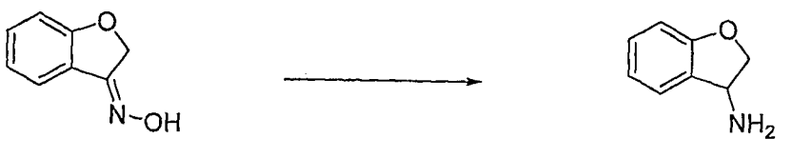
[00333] 2-fluoro-6-methoxybenzoyl chloride. Oxalyl chloride (0.56 mL, 6.4 mmol) was added to the solution of 1.0 g (5.9 mmol) 2-fluoro-6-methoxybenzoic acid in 5 mL anhydrous CH_2Cl_2. Then a drop of DMF was added. After one hour, when the slow bubbling was ceased, volatiles were removed under reduced pressure to afford 1.1 g (95%) acid chloride as pale-yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (q, 1H), 6.7-6.8 (m, 2H), 3.9 (s, 3H).

[00334] 4-fluorobenzofuran-3(2H)-one. The yellow (trimethylsilyl)diazomethane ether solution (2.0 M, 3.7 mL) was added to 0.57 g (3.0 mmol) above acid chloride with stirring. After 3 hours, solvent was evaporated. The yellow residue was dissolved in 3 mL acetic acid (strong gas and heat evolution, used a water bath to cool the flask for a minute), and stirred for 15 min at room temperature. The solvents were removed under vacuum, and the red residue was taken into 2 mL CH_2Cl_2, washed with water twice, then brine, and dried over Na_2SO_4. This crude product was purified by column chromatography (eluting with 10% EtOAc in hexanes) to give 0.24 g (53%) 4-

fluorobenzofuran-3(2H)-one as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (m, 1H), 6.92 (br d, 1H), 6.71 (t, 1H), 4.65 (s, 2H).

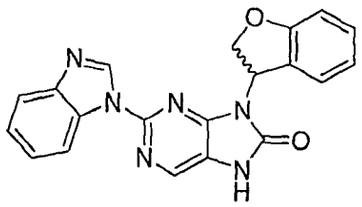
[00335] (Z)-4-fluorobenzofuran-3(2H)-one oxime. The above ketone (0.70g, 4.6 mmol) was dissolved in 5 ml ethyl alcohol, and then added 0.64 g (9.2 mmol) hydroxylamine hydrochloride and 0.75 g (9.2 mmol) sodium acetate. This suspension was brought to reflux for 1 hr. The mixture was cooled to room temperature and added 4 mL water to dissolve the excess reagents. Suction filtration, and then wash the solid cake with small amount of cold water provided 0.48 g (63%) desired oxime as white needle crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.38 (q, 1H), 6.6-6.8 (m, 2H), 5.21 (s, 2H).

[00336] 4-fluoro-2,3-dihydrobenzofuran-3-amine. The above oxime (0.48 g) was dissolved in 40 mL anhydrous THF under Argon. Fresh prepared aluminum amalgam (by dipping 1 g polished aluminum foil sequentially in 2% $HgCl_2$ aqueous solution, water, and finally THF) was added quickly and the mixture was refluxed for 24 hours under Argon. Shinny mercury beads appeared at the bottom of the flask. The mixture was allowed to cool to room temperature and filtered through a pad of celite. Flask and solid cake were washed with THF three times, then methanol three times. The combined filtrate was rotary evaporated to give 0.41g yellow solid as a mixture of approximately (determined by NMR) 20% desired amine with 80% starting oxime. This mixture was used for next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (q, 1H), 6.5-6.7 (m, 2H), 4.8-4.9 (m, 1H), 4.69 (t, 1H), 4.2-4.3 (m, 1H).



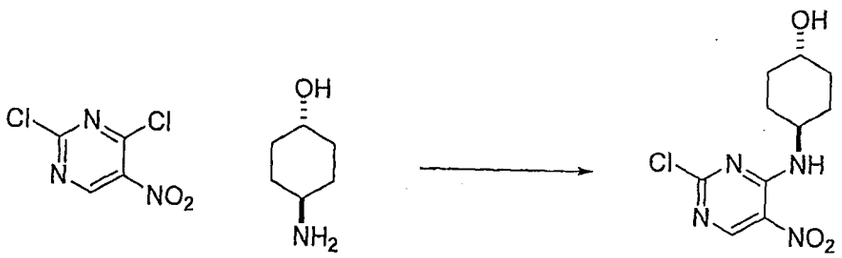
[00337] 2,3-dihydrobenzofuran-3-amine. To the solution of benzofuran-3(2H)-one oxime (1.0 g, obtained from commercially available benzofuran-3(2H)-one via the

procedure outlined for the synthesis of 4-fluorobenzofuran-3(2H)-one oxime from 4-fluorobenzofuran-3(2H)-one) in 50 mL MeOH, 10% Palladium on active carbon (0.1 g) was added. The mixture was evacuated then filled with H_2 three times. Finally the oxime was reduced under a H_2 balloon for 24 hours. The mixture was filtered through a pad of celite, and the cake was washed with MeOH twice. After removing the solvents under vacuum, 0.99 g brown-yellow residue was obtained as the desired amine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 1H), 7.19 (t, 1H), 6.94 (t, 1H), 6.82 (d, 1H), 4.5-4.7 (m, 1H), 4.64 (s, 1H), 4.1-4.2 (m, 1H).

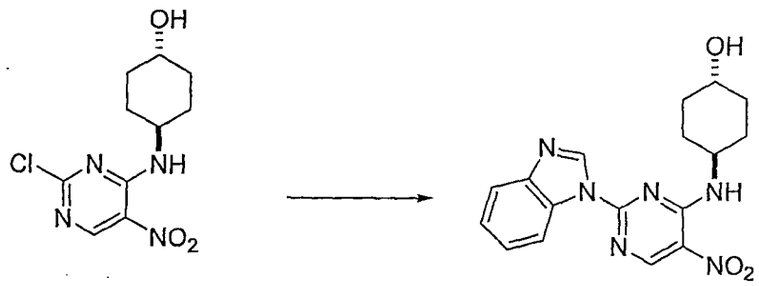


[00338] The above racemic 2-(1H-benzo[d]imidazol-1-yl)-9-(2,3-dihydrobenzofuran-3-yl)-7H-purin-8(9H)-one can be separated on chiral CHIRALCEL OD-H column (Cellulose tris(3,5-dimethylphenylcarbamate) on a 5μM silica-gel substrate) eluting with 85:15 hexanes:ethanol (both with 0.1% diethylamine). One enantiomer has a retention time of 25 min, the other one 33.5 min.

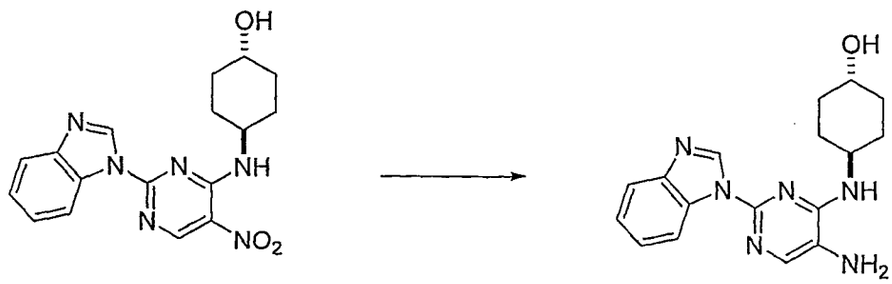
[00339] Synthesis of 2-(1H-Benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one.



[00340] *trans*-4-(2-Chloro-5nitropyrimidin-4-ylamino)cyclohexanol. A solution of 2,4-dicloro-5-nitropyrimidine (930 mg) in DCM (40 mL) was treated with DIEA (0.9 mL) and *trans*-4-aminocyclohexanol (345 mg) at -78 °C for 6 hours. The mixture was allowed to slowly warm to room temperature and stirred for 12 more hours. The solvent was evaporated and the crude mixture was purified by silica gel chromatography (DCM:EtOAc 70:30) to provide 630 mg of the title compound.



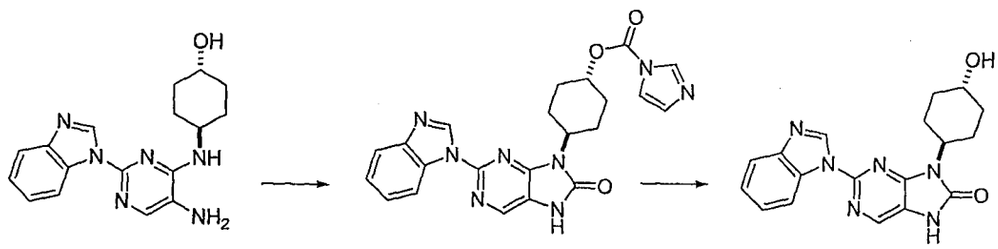
[00341] *trans*-4-(2-(1H-Benzo[d]imidazol-1-yl)-5-nitropyrimidin-4-ylamino)cyclohexanol. A mixture of *trans*-4-(2-chloro-5nitropyrimidin-4-ylamino)cyclohexanol (310 mg), benzimidazole (390 mg), and potassium carbonate (0.5 g) was heated in acetonitrile at 60 °C for 2 hours. The mixture was concentrated onto silicon gel and purified by column chromatography (DCM:EtOAc:MeOH 70:22:8) to give 350 mg of the title compound.



[00342] *trans*-4-(5-Amino-2-(1H-benzo[d]imidazol-1-yl)pyrimidin-4-ylamino)cyclohexanol. A solution of *trans*-4-(2-(1H-benzo[d]imidazol-1-yl)-5-nitropyrimidin-4-ylamino)cyclohexanol (162 mg) in THF (20ml) was treated with a

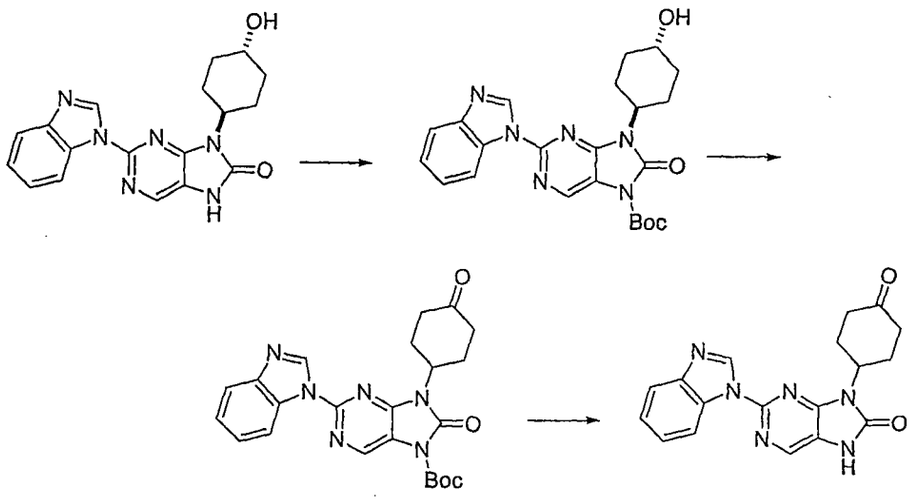
solution of sodium hydrosulfite (500 mg) and NaHCO3 (500 mg) in 20 mL of water and stirred for 25 minutes. The mixture was diluted with 200 mL EtOAc and washed twice with saturated sodium chloride. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 150 mg of the title compound.

[00343] *trans*-4-(2-(1H-Benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexyl 1H-imidazole-1-carboxylate. A solution of *trans*-4-(5-amino-2-(1H-benzo[d]imidazol-1-yl)pyrimidin-4-ylamino)cyclohexanol (150 mg) in DCM (15mL) was treated with carbonyldiimidazole (250 mg) overnight. The mixture was diluted with 100 mL of DCM and washed with brine once, then twice with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography purification (DCM:EtOAc;MeOH 70:22:8) provided 30 mg of the title compound.



[00344] 2-(1H-Benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one. *trans*-4-(2-(1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexyl 1H-imidazole-1-carboxylate (30 mg) was dissolved in DMSO (6 mL) and treated with 1N HCl (5 ml) at 50 °C for 3 hours. The mixture was diluted with EtOAc and washed with brine three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to obtain 16 mg of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ10.0 (s, 1H), 8.9(dd, 1H), 8.2 (s, 1H), 7.9 (dd, 1H), 7.6 (dd, 2H), 4.4 (m, 1H), 4.1 (s, 1H), 2.9 (m, 2H), 2.0 (m, 2H), 1.6 (m, 4H).

[00345] Synthesis of 2-(1H-Benzo[d]imidazol-1-yl)-9-(4-oxocyclohexyl)-7H-purin-8(9H)-one.

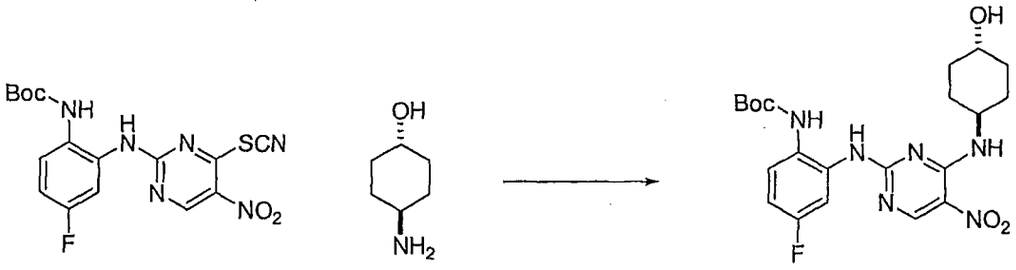


[00346] *tert*-Butyl 2-(1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-8-oxo-8,9-dihydropurine-7-carboxylate. Crude 2-(1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one (16 mg) was dissolved in DCM and treated with Boc_2O (150 mg) and Et_3N (1 ml). The mixture was stirred for 2 hours, then diluted with DCM and washed 3 times with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography column (DCM:EtOAc:MeOH, 70:25:5) provided 17 mg of the title compound. A pure sample of the starting material, 2-(1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one, could be obtained by deprotection of the title compound with 1:1 TFA / DCM for one hour, and then treating the resulting material with 10% methanolic HCl for another hour followed by concentration *in vacuo*.

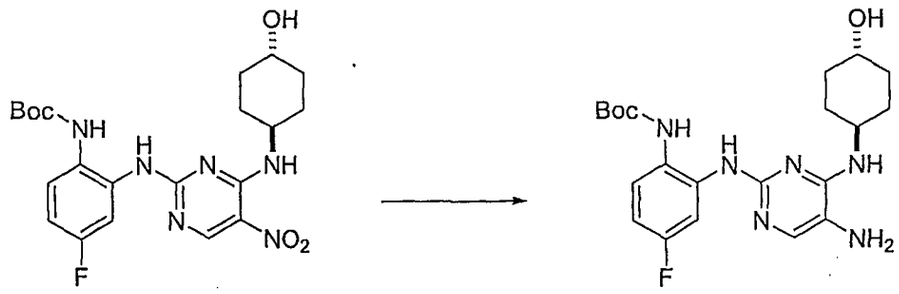
[00347] 2-(1H-Benzo[d]imidazol-1-yl)-9-(4-oxocyclohexyl)-7H-purin-8(9H)-one. A solution of oxalyl chloride (6.4 mg) in DCM (0.5 ml) was cooled to – 60 °C and treated with a solution of DMSO (8 mg) in DCM (0.5 ml). The reaction mixture was stirred for 2 minutes, then treated with a solution of *tert*-butyl 2-(1H-

benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-8-oxo-8,9-dihydropurine-7-carboxylate (4 mg) in DCM (0.5 ml). After 15 minutes, triethylamine (0.4 mL) was added and the mixture was stirred at room temperature for 30 minutes. The mixture was diluted with 10 mL DCM and washed with 15 mL of water. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to provide 2.3 mg of *tert*-butyl 2-(1H-benzo[d]imidazol-1-yl)-8-oxo-9-(4-oxocyclohexyl)-8,9-dihydropurine-7-carboxylate, which was deprotected with TFA/DCM (6 ml, 1:1) for 1 h. The mixture was concentrated and the residue was triturated with ethyl ether to provide 1.8 mg of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.5(dd, 1H), 8.4 (s, 1H), 7.9 (dd, 1H), 7.4 (m, 2H), 4.9 (m, 1H), 3.0 (m, 2H), 2.6 (m, 4H), 2.3(m, 2H).

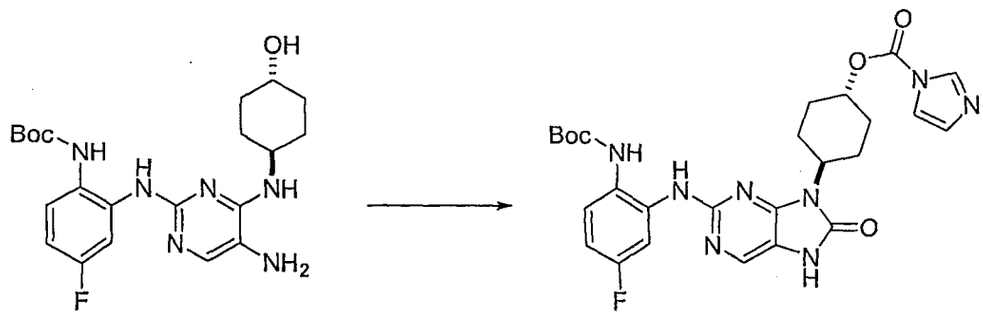
[00348] Synthesis of 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one.



[00349] *tert*-Butyl 4-fluoro-2-(4-(*trans*-4-hydroxycyclohexylamino)-5-nitropyrimidin-2-ylamino)phenylcarbamate. Potassium carbonate (105 mg) was added to a stirred mixture of *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)phenyl-carbamate (101 mg) in acetonitrile (5 ml) followed by the addition of *trans*-4-hydroxycyclohexylamine (44 mg). The reaction mixture was stirred for 16 hours, then diluted with DCM and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 110 mg of the title compound.

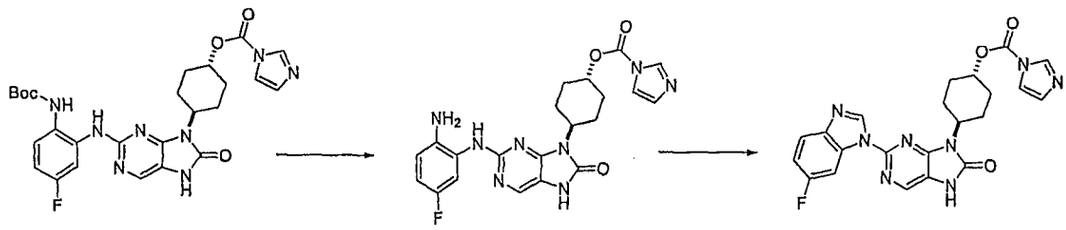


[00350] *tert*-Butyl 2-(5-amino-4-(*trans*-4-hydroxycyclohexylamino)pyrimidin-2-ylamino)-4-fluorophenylcarbamate. A solution of *tert*-butyl 4-fluoro-2-(4-(*trans*-4-hydroxycyclohexylamino)-5-nitropyrimidin-2-ylamino)phenylcarbamate (110 mg) in THF (30 mL) was treated with a mixture containing sodium hydrosulfite (600 mg in 20 ml H2O) and sodium bicarbonate (10 ml, saturated). The resulting mixture was stirred for 5 minutes during which the color changed from yellow to almost colorless. Saturated sodium chloride was added and the mixture was extracted with EtOAc twice. The combined organic layers were washed with saturated sodium chloride and separated. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 111 mg of the title compound.

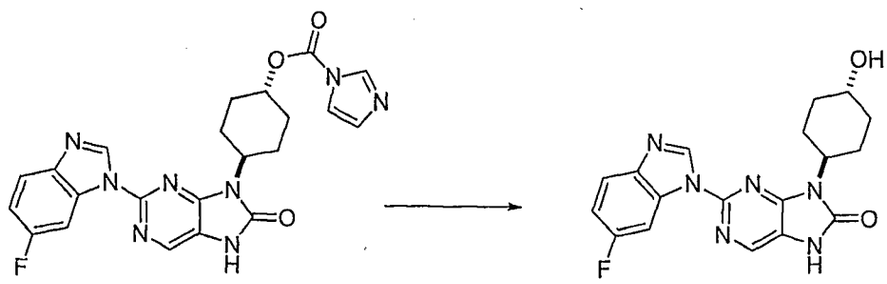


[00351] *trans*-4-(2-(2-(*tert*-Butoxycarbonyl)-5-fluorophenylamino)-8-oxo-7,8-dihydropurin-9-yl)cyclohexyl 1H-imidazole-1-carboxylate. A solution of *tert*-butyl 2-(5-amino-4-(*trans*-4-hydroxycyclohexylamino)pyrimidin-2-ylamino)-4-fluorophenylcarbamate (111 mg) in DCM (10 mL) was treated with

carbonyldiimidazole overnight. The reaction mixture was diluted with DCM (10 ml) and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography provided 100 mg of the title compound.



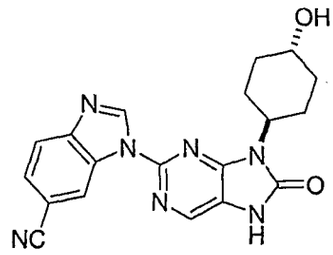
[00352] *trans*-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexyl 1H-imidazole-1-carboxylate. A solution of *trans*-4-(2-(2-(*tert*-butoxycarbonyl)-5-fluorophenylamino)-8-oxo-7,8-dihydropurin-9-yl)cyclohexyl 1H-imidazole-1-carboxylate (100 mg) in TFA/DCM (18 ml, 1:1) was stirred for 1 hour. The mixture was concentrated *in vacuo* to provide 95 mg of material. This material was dissolved in THF (30 ml) and treated with $CH(OCH_3)_3$ (1 ml) followed by p-toluenesulfonic acid (5 mg). The mixture was stirred for 3 h, diluted with EtOAc (100 ml) and washed three times with brine. The organic layer was dried over Na_2SO_4 and the solvent was concentrated to provide 22 mg of the title compound.



[00353] 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one. A solution of *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexyl 1H-imidazole-1-carboxylate (30 mg) in DMSO

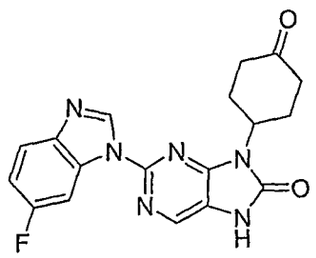
(5 ml) was treated with concentrated HCl (1 ml). The mixture was heated at 50 °C for 3 hours. The mixture was diluted with EtOAc and made basic with 3N NaOH (10 ml) The organic layer was washed three times with brine, dried over Na_2SO_4, filtered, and concentrated to provide 20 mg of the title compound. ^{1}H-NMR (300 MHz, CD_3OD) δ 10.5 (s, 1H), 8.8 (dd, 1H), 8.6 (s, 1H), 8.1 (dd, 1H), 7.7 (td, 1H), 4.6 (m, 1H), 4.7 (m, 1H), 4.0 (m, 1H), 2.7 (m, 2H), 2.3 (m, 2H), 2.1 (m, 2H), 1.7 (m, 2H).

[00354] Synthesis of 3-(9-(*trans*-4-Hydroxycyclohexyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile.



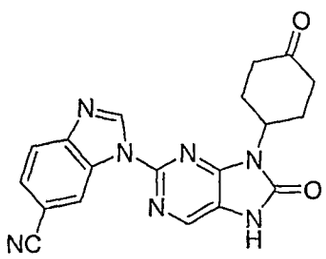
The title compound could be obtained from 4-(2,4-dimethoxybenzylamino)-3-(4,5-diaminopyrimidin-2-ylamino)benzonitrile using the same procedures outlined for the synthesis of 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one from *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)phenylcarbamate. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.8 (s, 1H), 9.1(s, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 7.8 (d, 1H), 4.4 (m, 1H), 3.8 (m, 1H), 2.5 (q, 2H), 2.2 (d, 2H), 1.9 (d, 2H), 1.5 (q, 2H).

[00355] Synthesis of 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(4-oxocyclohexyl)-7H-purin-8(9H)-one.



[00356] The title compound could be obtained from 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one using the same procedure outlined for the synthesis of 2-(1H-benzo[d]imidazol-1-yl)-9-(4-oxocyclohexyl)-7H-purin-8(9H)-one from 2-(1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.8 (s, 1H), 9.2(s, 1H), 9.1 (s, 1H), 7.6 (dd, 1H), 7.8 (dd, 1H), 4.8 (m, 1H), 2.8 (m, 2H), 2.5 (m, 4H), 2.1 (m, 2H).

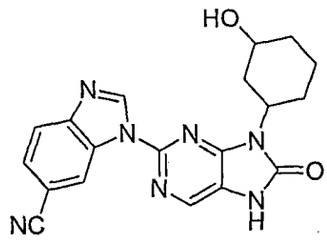
[00357] Synthesis of 3-(8-Oxo-9-(4-oxocyclohexyl)-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile.



[00358] The title compound could be obtained from 3-(9-(*trans*-4-hydroxycyclohexyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile using the same procedures outlined for the synthesis of 2-(1H-benzo[d]imidazol-1-yl)-9-(4-oxocyclohexyl)-7H-purin-8(9H)-one from 2-(1H-

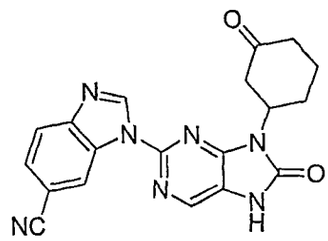
benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.3 (s, 1H), 9.2(s, 1H), 8.5 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 4.6 (m, 1H), 2.9 (m, 2H), 2.6 (m, 4H), 2.2 (m, 2H).

[00359] Synthesis of 3-(9-(3-Hydroxycyclohexyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile.



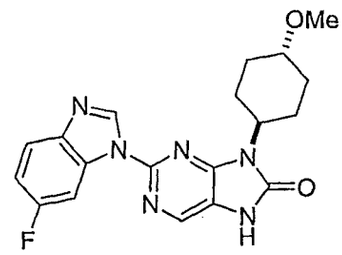
The title compound could be obtained from 4-(2,4-dimethoxybenzylamino)-3-(4,5-diaminopyrimidin-2-ylamino)benzonitrile and 3-hydroxycyclohexylamine using the same procedures outlined for the synthesis of 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one from *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)phenylcarbamate. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.4 (s, 1H), 9.2(s, 1H), 8.4 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 4.6 (m, 1H), 3.9 (m, 1H), 2.5 (m, 2H), 2.2 (m, 2H), 2.1 (m, 2H), 1.6 (m, 2H).

[00360] Synthesis of 3-(8-Oxo-9-(3-oxocyclohexyl)-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile.



The title compound could be obtained from 3-(9-(3-hydroxycyclohexyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile using the same procedures outlined for the synthesis of 2-(1H-benzo[d]imidazol-1-yl)-9-(4-oxocyclohexyl)-7H-purin-8(9H)-one from 2-(1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.2 (s, 1H), 8.6(s, 1H), 8.5 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 5.0 (m, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 2.9 (m, 2H), 2.6 (m, 2H), 2.3 (m, 2H).

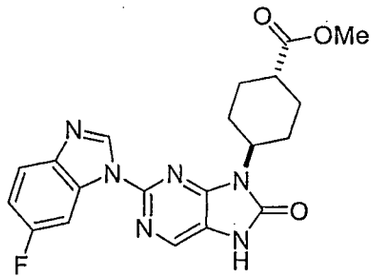
[00361] Synthesis of 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-methoxycyclohexyl)-7H-purin-8(9H)-one.



A solution of 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-7H-purin-8(9H)-one (112 mg) in DCM was treated with excess Boc_2O and triethylamine until TLC analysis indicated that the starting material had been consumed (4 hours). The mixture was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was dissolved in THF, treated with excess iodomethane, and then NaH (10 equivalents). The mixture was stirred for 6 hours and quenched by the addition of saturated ammonium chloride. The intermediate was extracted with EtOAc, dried, and concentrated. Silica gel chromatography (70:25:5 DCM:EtOAc:MeOH) provided pure *tert*-butyl 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-methoxycyclohexyl)-8-oxo-8,9-dihydropurine-7-carboxylate, which was deprotected in 1:1 TFA / DCM for 16 hours and concentrated *in vacuo* to obtain the title compound. The HCl salt was obtained by treating a methanolic solution (10

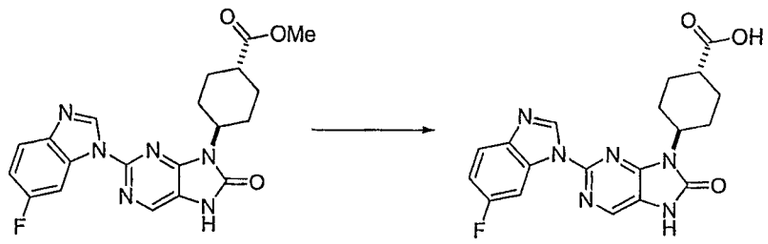
mL) with 0.5 mL of concentrated HCl followed by solvent evaporation. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.3(dd, 1H), 8.1 (s, 1H), 7.6 (dd, 1H), 7.1 (td, 1H), 4.4 (m, 1H), 3.8 (m, 1H), 2.5 (m, 2H), 2.1 (m, 2H), 1.9 (m, 2H), 1.5 (m, 2H).

[00362] Synthesis of *trans*-Methyl 4-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexanecarboxylate.



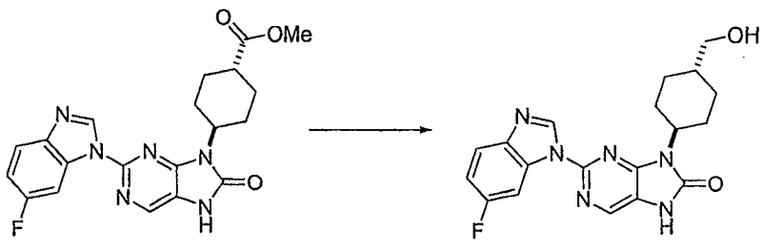
The title compound was obtained from *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidine-2-ylamino)phenylcarbamate and methyl *trans*-4-aminocyclohexanecarboxylate using procedures outline in Example 27. ^{1}H-NMR (300 MHz, $CDCl_3$) δ9.0 (s, 1H), 8.4(s, 1H), 8.3 (dd, 1H), 7.8 (dd, 1H), 7.2 (td, 1H), 4.5 (m, 1H), 2.6 (m, 3H), 2.3 (m, 2H), 2.0 (m, 2H), 1.7 (m, 2H).

[00363] Synthesis of *trans*-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexanecarboxylic acid.



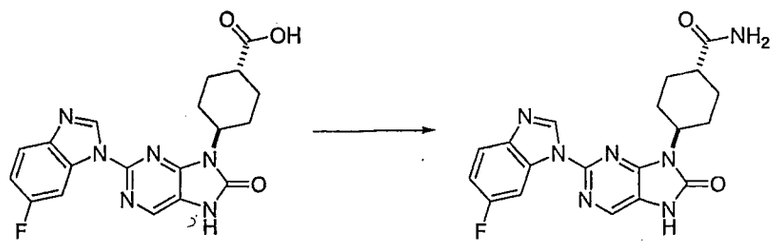
A solution of *trans*-methyl 4-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexanecarboxylate (5 mg) in THF was treated with an aqueous solution of KOH (35 mg) in 2 mL of water. The mixture was heated at 50 °C for 12 hours. The mixture was acidified with TFA and concentrated. Silica gel chromatography (60:30:10 DCM:EtOAc:MeOH) provided 4.3 mg of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.3(dd, 1H), 8.1 (s, 1H), 7.7 (dd, 1H), 7.1 (td, 1H), 4.3 (m, 1H), 2.4 (m, 3H), 2.2 (m, 2H), 1.9 (m, 2H), 1.6 (m, 2H).

[00364] Synthesis of 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-(hydroxymethyl)cyclohexyl)-7H-purin-8(9H)-one.



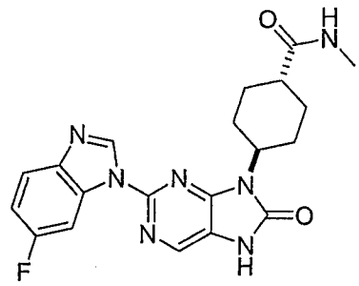
A solution of *trans*-methyl 4-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexanecarboxylate (6 mg) in DCM was treated with 10 equivalents of a 1 M THF solution of $LiAlH_4$ at -10 °C. The mixture was stirred at -10 °C for 12 hours and 0 °C for 2 more hours. The mixture was quenched with aqueous sodium bicarbonate and extracted with EtOAc. Silica gel chromatography provided 3.0 mg of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.3(dd, 1H), 8.1 (s, 1H), 7.7 (dd, 1H), 7.1 (td, 1H), 4.3 (m, 1H), 3.3 (d, 2H), 2.4 (m, 2H), 1.9 (m, 4H), 1.6 (m, 2H).

[00365] Synthesis of *trans*-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexanecarboxamide.



A suspension of *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexanecarboxylic acid (10 mg) in DCM was treated with 6 drops of DMF followed by 3 equivalents of oxalyl chloride. The mixture was stirred for 45 minutes, then it was sparged with an ammonia balloon for 10 minutes. The mixture was concentrated and purified by HPLC to provide 1.7 mg of the title compound. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.1 (s, 1H), 8.3 (dd, 1H), 8.2 (s, 1H) 7.7 (dd, 1H), 7.1 (td, 1H), 4.4 (m, 1H), 2.5 (m, 2H), 2.4 (m, 1H), 2.1 (m, 2H), 1.9 (m, 2H), 1.7 (m, 2H).

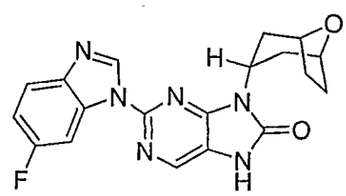
[00366] Synthesis of *trans*-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)-N-methylcyclohexanecarboxamide.



The title compound could be obtained from *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexane-carboxylic acid and 2 M methylamine in THF using the same procedure outlined for the synthesis of *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)cyclohexanecarboxamide. ^{1}H-NMR (300 MHz, $CDCl_3$ with 5 % CD_3OD) δ 9.0 (s,

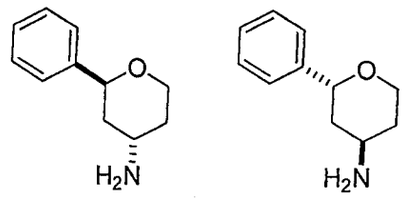
1H), 8.3 (dd, 1H), 8.2 (s, 1H), 7.7 (dd, 1H), 7.1 (td, 1H), 4.4 (m, 1H), 2.8 (s, 3H) 2.5 (m, 2H), 2.3 (m, 1H), 2.1 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H).

[00367] Synthesis of 9-(8-oxa-bicyclo[3.2.1]octan-3-yl)-2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-7H-purin-8(9H)-one.



The title compound was obtained from *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidine-2-ylamino)phenylcarbamate and 8-oxa-bicyclo[3.2.1]octan-3-amine (WO 2004/041161) using procedures outlined in Example 27. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.4 (bs, 1H), 9.0 (s, 1H), 8.4 (dd, 1H), 8.3 (s, 1H), 7.8 (dd, 1H), 7.1 (td, 1H), 4.9 (m, 1H), 4.6 (m, 2H), 2.9 (m, 2H), 2.2 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H).

[00368] Synthesis of (+/-)-2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-2-phenyl-tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one.

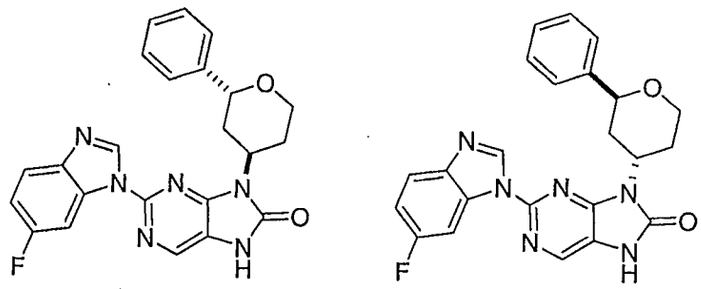


[00369] *trans*-2-Phenyl-tetrahydro-2H-pyran-4-amine. Sulfuric acid (80%, 16.5 g) was added dropwise at 0 °C to a mixture of but-3-en-1-ol (13.6 g) and benzaldehyde (10 g). After the addition the mixture was stirred at room temperature for 16 hours. The mixture was poured into ice water, made basic (pH 8-10) with 1 N NaOH, extracted with EtOAc, dried, and concentrated. Silica gel chromatography provided 9 g of *cis*-2-phenyl-tetrahydro-2H-pyran-4-ol.

[00370] A solution of *cis*-2-phenyltetrahydro-2H-pyran-4-ol (1 g) in DCM (20 mL) was cooled in an ice-salt water bath and treated with DIEA (2.2 g) and methanesulfonyl chloride (0.7 g) for 2 hours. The mixture was diluted with DCM (50 mL) and washed with water and brine. The organic layer was dried and concentrated. Preparative TLC provided 0.9 g of *cis*-2-phenyl-tetrahydro-2H-pyran-4-yl methanesulfonate.

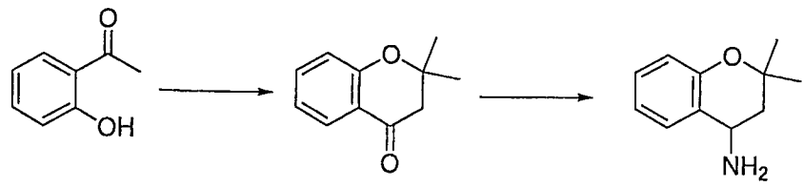
[00371] A solution of *cis*-2-phenyl-tetrahydro-2H-pyran-4-yl methanesulfonate (0.8 g) in DMF (10 mL) was treated with sodium azide (0.8 g) and heated at 100 °C for 4 hours. The mixture was diluted with DCM (50 mL) and washed with water and brine. The organic layer was dried and concentrated. Preparative TLC provided 0.5 g of *trans*-4-azido-2-phenyl-tetrahydro-2H-pyran.

[00372] The title compound was obtained *via* catalytic hydrogenation (Pd-C, H_2) of *trans*-4-azido-2-phenyl-tetrahydro-2H-pyran.

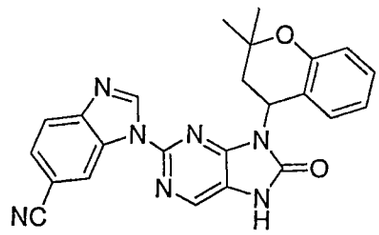


(+/-)-2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(*trans*-2-phenyl-tetrahydro-2H-pyran-4-yl)-7H-purin-8(9H)-one. The title compound was obtained from *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidine-2-ylamino)phenylcarbamate and *trans*-2-phenyl-tetrahydro-2H-pyran-4-amine using procedures outlined in Example 27. ^{1}H-NMR (300 MHz, $CDCl_3$ with 5 % CD_3OD) δ 9.0 (s, 1H), 8.2 (dd, 1H), 8.1 (s, 1H), 7.6 (dd, 1H), 7.4 (d, 2H), 7.3 (t, 2H), 7.2 (t, 1H), 7.0 (td, 1H), 5.2 (br s, 1H), 4.7 (m, 1H), 3.9-3.8 (m, 1H), 3.7 (td, 1H), 3.1-2.8 (m, 2H), 2.4 (br d, 1H), 1.7 (br d, 1H).

[00373] Synthesis of 3-(9-(2,2-Dimethylchroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile.



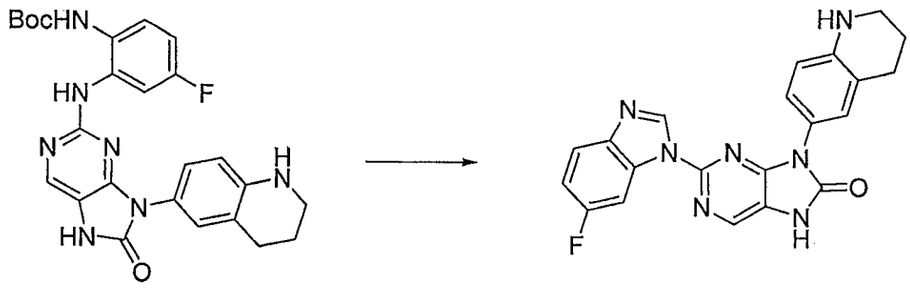
[00374] 2,2-Dimethylchroman-4-amine. A solution of 2'-hydroxyacetophenone (5.0 mL), acetone (4.7 mL), and pyrrolidine (5.4 mL) in 150 mL of methanol was stirred for 66 hours. The mixture was concentrated and treated with aqueous HCl (pH < 1). The acidic layer was extracted twice with ethyl ether, which was dried and concentrated to provide 2,2-dimethylchroman-4-one. The 2,2-dimethylchroman-4-one was dissolved in 300 mL of methanol and treated with ammonium acetate (65 g) and sodium cyanoborohydride (2.5 g) for 24 hours. The resulting mixture was concentrated to 100 mL and diluted with 300 mL water. Concentrated HCl was carefully added until the pH was less than 1 and the acidic mixture was extracted with ethyl ether. The acidic phase was made basic with KOH and then extracted twice with ethyl ether. The basic extracts were dried and concentrated to provide the title compound.



[00375] 3-(9-(2,2-Dimethylchroman-4-yl)-8-oxo-8,9-dihydro-7H-purin-2-yl)-3H-benzo[d]imidazole-5-carbonitrile. The title compound was obtained from 4-(2,4-dimethoxybenzylamino)-3-(4,5-diaminopyrimidin-2-ylamino)benzonitrile and 2,2-

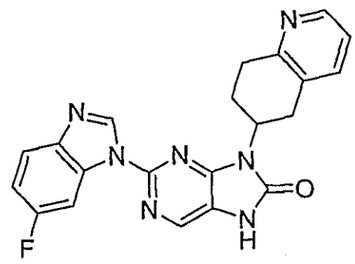
dimethylchroman-4-amine using procedures outlined in Example 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.6 (s, 1H), 9.0 (s, 1H), 8.5 (bs, 1H), 8.3 (s, 1H), 7.8 (d, 1H), 7.6 (dd, 1H), 7.2 (m, 2H), 6.8 (d, 1H), 6.7 (td, 1H), 5.9 (dd, 1H), 2.9 (t, 1H), 2.2 (dd, 1H), 1.6 (s, 3H), 1.5 (s, 3H).

[00376] Synthesis of 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(1,2,3,4-tetrahydroquinolin-6-yl)-7H-purin-8(9H)-one.



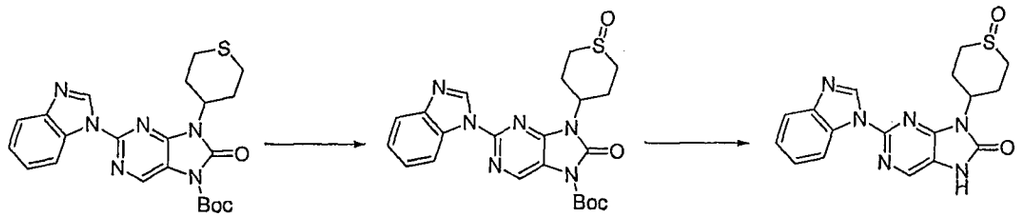
A solution of *tert*-butyl 4-fluoro-2-(8-oxo-9-(1,2,3,4-tetrahydroquinolin-6-yl)-8,9-dihydro-7H-purin-2-ylamino)phenylcarbamate (obtained from *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidine-2-ylamino)phenylcarbamate and 1,2,3,4-tetrahydroquinolin-6-amine (*J. Org. Chem.* (2002), *67*, 7890) using procedures outlined in Example 27) was stirred for 45 minutes in 1:1 TFA / DCM and concentrated to afford 2-(2-amino-5-fluorophenylamino)-9-(1,2,3,4-tetrahydroquinolin-6-yl)-7H-purin-8(9H)-one. The 2-(2-amino-5-fluorophenylamino)-9-(1,2,3,4-tetrahydroquinolin-6-yl)-7H-purin-8(9H)-one was stirred for 15 minutes in trimethylorthoformate and concentrated to afford 6-(2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-8-oxo-7,8-dihydropurin-9-yl)-3,4-dihydroquinoline-1(2H)-carbaldehyde, which was purified by silica gel chromatography (2→5% MeOH in DCM). This material was deformylated by refluxing for 1 hour in 11:2 1 M HCl:MeOH to provide the title compound as the HCl salt. ^{1}H-NMR (300 MHz, CD_3OD) δ 10.0 (s, 1H), 8.4 (s, 1H), 8.4 (dd, 1H), 7.8 (dd, 1H), 7.8 (s, 1H), 7.8 (d, 1H), 7.5 (d, 1H), 7.4 (td, 1H), 3.6 (dd, 2H), 3.1 (t, 2H), 2.2 (m, 2H).

[00377] Synthesis of 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-(5,6,7,8-tetrahydroquinolin-6-yl)-7H-purin-8(9H)-one.



The title compound was obtained from *tert*-butyl 4-fluoro-2-(5-nitro-4-thiocyanatopyrimidine-2-ylamino)phenylcarbamate and 5,6,7,8-tetrahydroquinolin-6-amine (*J. Org. Chem.* (2002), *67*, 7890) using procedures outlined in Example 27. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.3 (s, 1H), 8.6 (d, 1H), 8.5 (dd, 1H), 8.1 (dd, 1H), 7.9 (dd, 1H), 7.4 (td, 1H), 5.2 (m, 1H), 4.2 (dd, 1H), 3.6 (m, 3H), 3.2 (m, 1H), 2.6 (m, 1H).

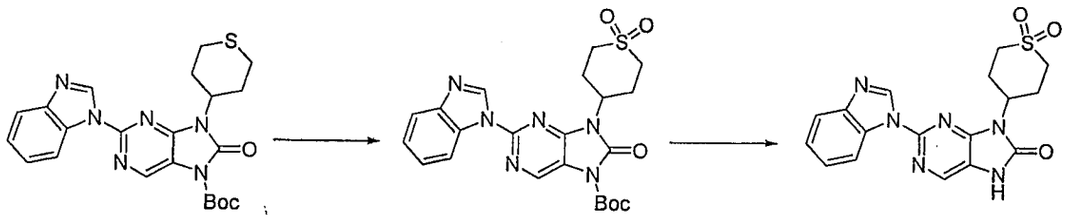
[00378] Synthesis of 2-(1H-Benzo[d]imidazol-1-yl)-9-(tetrahydro-1-oxido-2H-thiopyran-4-yl)-7H-purin-8(9H)-one.



[00379] A solution of *tert*-butyl 2-(1H-benzo[d]imidazol-1-yl)-8-oxo-9-(tetrahydro-2H-thiopyran-4-yl)-8,9-dihydropurine-7-carboxylate (8 mg, obtained from tetrahydro-thiopyran-4-ylamine using procedures outlined in Example 16 followed by protection using the procedure outline for the synthesis of *tert*-butyl 2-(1H-benzo[d]imidazol-1-yl)-9-(*trans*-4-hydroxycyclohexyl)-8-oxo-8,9-dihydropurine-7-carboxylate) in MeOH/H_2O (10ml, 1:1) was treated with KIO_4 (50 mg) and stirred for 3 hours. The

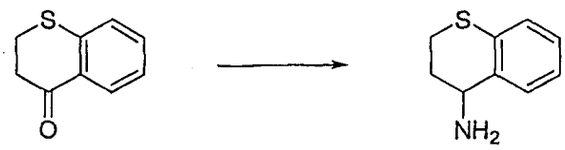
reaction mixture was diluted with 10 ml of saturated $NaHCO_3$ and extracted 3 times with DCM. The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography column purification (DCM:EtOAc;MeOH 75:25:5) provided 5.6 mg of *tert*-butyl 2-(1H-benzo[d]imidazol-1-yl)-8-oxo-9-(tetrahydro-1-oxido-2H-thiopyran-4-yl)-8,9-dihydropurine-7-carboxylate. This material was treated with TFA/DCM (6 ml, 1:1) for 1 hour and concentrated. Trituration with Et_2O provided 3.3 mg of the title compound. ^1H NMR (300 MHz $CDCl_3$) δ 9.1 (br, 1H), 8.5(m, 1H), 8.2 (s, 1H), 7.8 (m, 1H), 7.4 (m, 2H), 4.6 (m, 1H), 3.6 (m, 2H), 2.9 (m, 4H), 2.2 (m, 2H).

[00380] Synthesis of 2-(1H-Benzo[d]imidazol-1-yl)-9-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)-7H-purin-8(9H)-one.

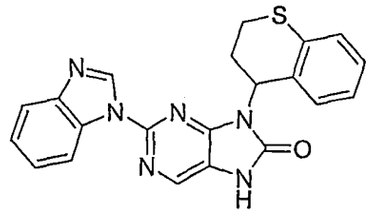


A solution of *tert*-butyl 2-(1H-benzo[d]imidazol-1-yl)-8-oxo-9-(tetrahydro-2H-thiopyran-4-yl)-8,9-dihydropurine-7-carboxylate (8 mg) in DCM (10ml) was treated with MCPBA (13 mg) and stirred for 16 hours. The mixture was washed 3 times with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography column purification (DCM:EtOAc;MeOH 75:25:5) provided 2.2 mg of *tert*-butyl 2-(1H-benzo[d]imidazol-1-yl)-8-oxo-9-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)-8,9-dihydropurine-7-carboxylate. This material was treated with TFA/DCM (6 ml, 1:1) for 1 hour and concentrated. Trituration with Et_2O provided 1.3 mg of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 9.2 (br, 1H), 8.7 (d, 1H), 7.8 (d, 1H), 7.5 (t, 1H), 7.4 (t, 1H), 4.6 (m, 1H), 3.0-3.5 (m, 6H), 2.2 (m, 2H).

[00381] Synthesis of 2-(1H-Benzo[d]imidazol-1-yl)-9-(thiochroman-4-yl)-7H-purin-8(9H)-one.



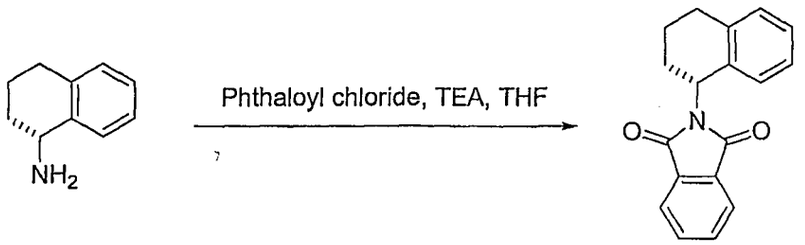
[00382] Thiochroman-4-amine. To a solution of thiochroman-4-one (1.6 g) in EtOH (100 ml) was added NH_4OAc (8.2 g), the mixture was heated at 50 °C for 35 minutes then cooled to room temperature and treated with $Na(CN)BH_4$ (0.96 g). The mixture was stirred at room temperature for 64 hours and the reaction solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed 4 times with 4N HCl. The combined aqueous washes were made basic with 3N NaOH, then extracted 5 times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to provide 1.4 g of the title compound.



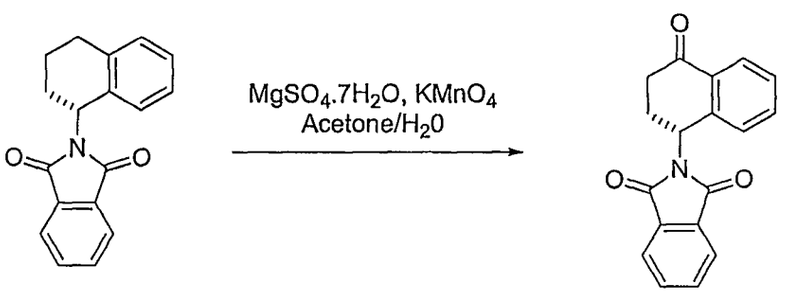
[00383] 2-(1H-Benzo[d]imidazol-1-yl)-9-(thiochroman-4-yl)-7H-purin-8(9H)-one. The title compound was synthesized from thiochroman-4-amine using the procedures outlined in Example 16. ^1H NMR (300 MHz, CD_3OD) δ 9.1 (s, 1H), 8.5 (s, 1H), 8.3 (m, 1H), 7.8 (m, 1H), 7.4 (m, 3H), 7.3 (m, 1H), 7.0-7.2 (m, 2H), 6.0 (m, 1H), 3.4 (m, 2H), 3.1 (m, 1H), 2.6 (m, 1H).

[00384] Synthesis of 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-((*R*)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one, 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-((1*R*,4*R*)-4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one,

and 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-((1*R*,4*S*)-4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one.

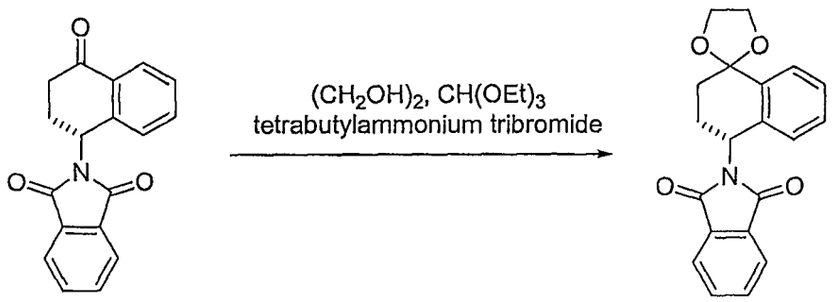


[00385] (*R*)-2-(1,2,3,4-Tetrahydronaphthalen-1-yl)isoindoline-1,3-dione. To a solution of (*R*)-1,2,3,4-tetrahydro-1-naphthylamine (6.0 g) in THF (150 mL) at 0 °C was added TEA (18.5 mL) and phthaloyl chloride (8.2 g), and the resultant mixture was stirred at room temperature overnight and 70 °C for 3 h. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The resulting crude was chromatographed on silica gel (EtOAc/hexane, 5/95 to 30/70) to afford 8.2 g of the title compound.

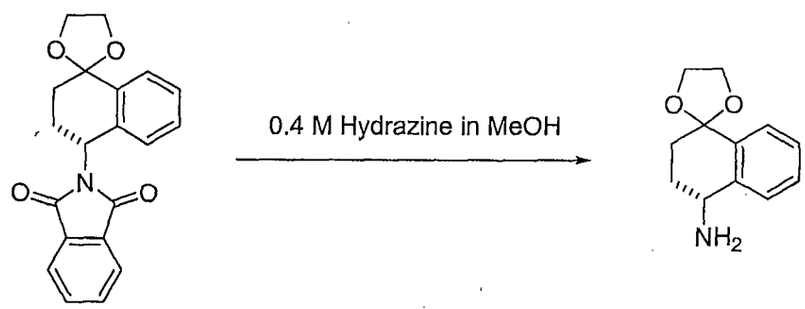


[00386] (*R*)-2-(4-Oxo-1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1,3-dione. To a solution of (*R*)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1,3-dione (3.9 g) in acetone (60 mL) at 0 °C was added $MgSO_4 \cdot 7H_2O$ (11.5 g) and water (20 mL). Then $KMnO_4$ (11.5 g) was added portionwise over the period of 2 h and stirring continued at room temperature overnight. The brown solid was filtered off and the filtrate treated with saturated sodium metabisulfite, filtered, and extracted with CH_2Cl_2. The

combined organic layer was washed with distilled water and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant was chromatographed on silica gel (EtOAc/hexane, 25/75) to afford 0.14 g of the title compound.

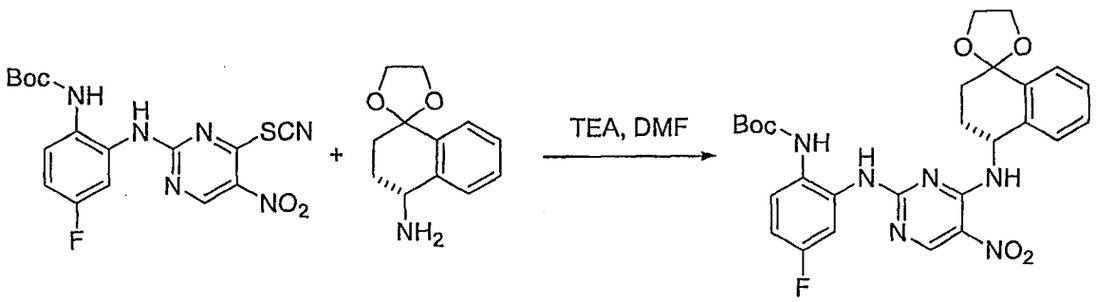


[00387] 1,3-Dioxolane of (*R*)-2-(4-oxo-1,2,3,4-Tetrahydronaphthalen-1-yl)isoindoline-1,3-dione. To the mixture of of (*R*)-2-(4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1,3-dione (138 mg), triethyl orthoformate (0.3 mL), and 1,2-ethanediol (1.5 mL) was added tetrabutylammonium tribromide (12 mg). The reaction mixture was stirred at room temperature overnight and heated at 90 °C for 3 h. After cooling, the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by PTLC (EtOAc/hexane, 1/2) to afford 150 mg of the title compound.

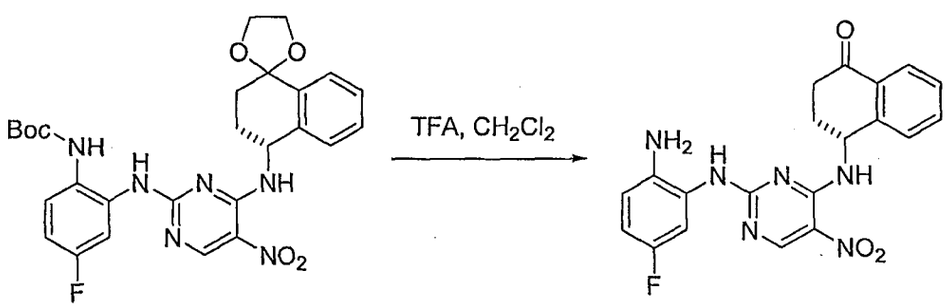


[00388] 1,3-Dioxolane of (*R*)-4-amino-3,4-dihydronaphthalen-1(2H)-one. A solution of 1,3-dioxolane of (*R*)-2-(4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1,3-dione (145 mg) in 0.4 M methanolic hydrazine (40 mL) was stirred

at room temperature overnight. The solvent and excess hydrazine were evaporated and a small amount of CH_2Cl_2 was added to the residue. The white solid was filtered off and the filtrate concentrated in vacuo to afford 85 mg of the title compound.

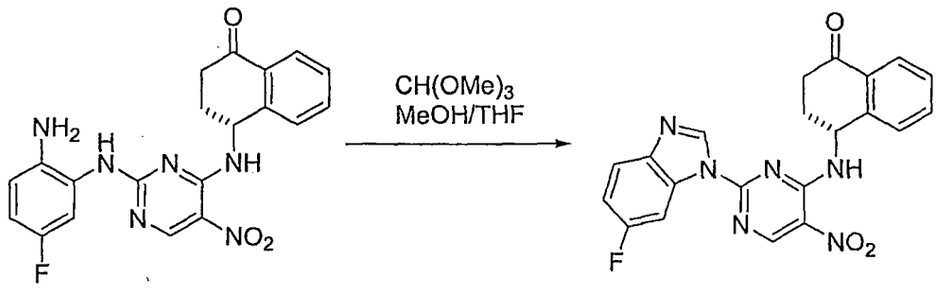


[00389] 1,3-Dioxolane of (*R*)-*tert*-butyl 4-fluoro-2-(5-nitro-4-(4-oxo-1,2,3,4-tetrahydronaphthalen-1-ylamino)pyrimidin-2-ylamino)phenylcarbamate. A solution of *tert*-butyl 4 fluoro-2-(5-nitro-4-thiocyanatopyrimidin-2-ylamino)phenylcarbamate (170 mg), 1,3-Dioxolane of (*R*)-4-amino-3,4-dihydronaphthalen-1(2H)-one (85 mg), and TEA (0.2 mL) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by PTLC (EtOAc/hexane, 50/50) to afford 150 mg of the title compound.

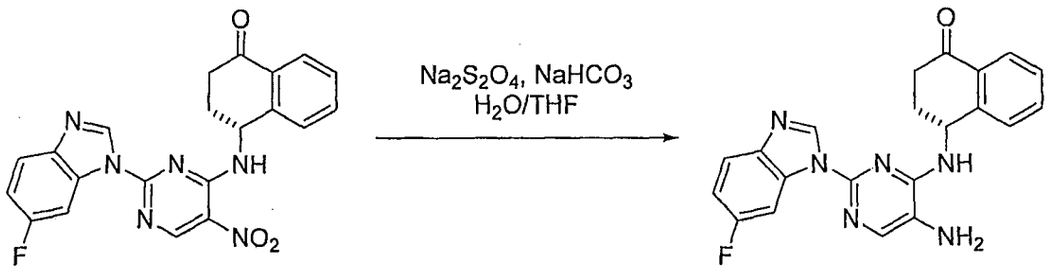


[00390] (*R*)-4-(2-(2-Amino-5-fluorophenylamino)-5-nitropyrimidin-4-ylamino)-3,4-dihydronaphthalen-1(2H)-one. A solution of 1,3-dioxolane of (*R*)-*tert*-butyl 4-fluoro-

2-(5-nitro-4-(4-oxo-1,2,3,4-tetrahydronaphthalen-1-ylamino)pyrimidin-2-ylamino)phenylcarbamate (145 mg) and TFA (2.5 mL) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. Volatiles were removed in vacuo and the crude (120 mg) was subjected to the next step without further purification.

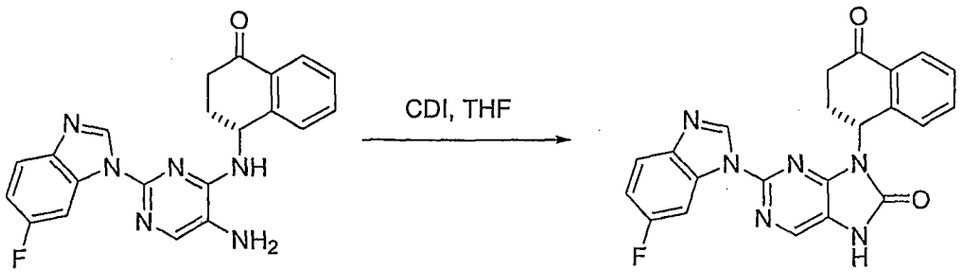


[00391] (4*R*)-4-(2-(6-Fluoro -1H-benzo[d]imidazol-1-yl)-5-nitropyrimidin-4-ylamino)-3,4-dihydronaphthalen-1(2H)-one. A solution of (*R*)-4-(2-(2-amino-5-fluorophenylamino)-5-nitropyrimidin-4-ylamino)-3,4-dihydronaphthalen-1(2H)-one (120 mg) and $CH(OMe)_3$ (2.5 mL) in MeOH/THF (2.5 mL/10 mL) was stirred at room temperature overnight. Volatiles were removed in vacuo and the residue was purified by PTLC (EtOAc) to afford 80 mg of the title compound.

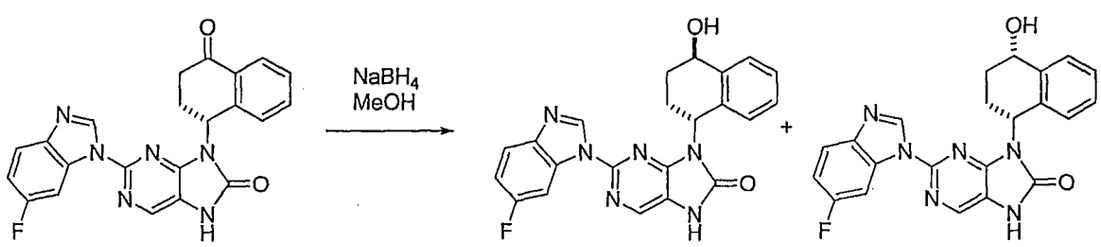


[00392] (4*R*)-4-(5-Amino-2-(6-fluoro -1H-benzo[d]imidazol-1-yl)pyrimidin-4-ylamino)-3,4-dihydronaphthalen-1(2H)-one. To the solution of (4*R*)-4-(2-(6-fluoro -1H-benzo[d]imidazol-1-yl)-5-nitropyrimidin-4-ylamino)-3,4-dihydronaphthalen-1(2H)-one (80 mg) in THF (10 mL) was added $Na_2S_2O_4$ (480 mg) and $NaHCO_3$ (240 mg) in H_2O (10 mL), and stirring continued at room temperature for 1.5 h. The

reaction mixture was diluted with CH_2Cl_2, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude (32 mg) was subjected to the next step without further purification.



[00393] 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-((*R*)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one. A solution of (4*R*)-4-(5-amino-2-(6-fluoro -1H-benzo[d]imidazol-1-yl)pyrimidin-4-ylamino)-3,4-dihydronaphthalen-1(2H)-one (32 mg) and CDI (100 mg) in THF (6 mL) was stirred at room temperature overnight and refluxed for 2.5 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC to afford 9 mg of the title compound as the TFA salt. ^{1}H NMR (CD_3OD) δ9.20 (s, 1H), 8.36 (s, 1H), 8.20 (m, 1H), 7.68 (m, 1H), 7.58-7.47 (m, 3H), 7.20-7.14 (m, 2H), 6.10 (m, 1H), 3.09-2.93 (m, 3H), 2.49 (m, 1H); MS (MH^+) 415.1.



[00394] 2-(6-Fluoro-1H-benzo[d]imidazol-1-yl)-9-((1*R*,4*R*)-4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one and 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-((1*R*,4*S*)-4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-

purin-8(9H)-one. To a solution of 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-((R)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one (6 mg) in MeOH (2.5 mL) at 0 °C was added $NaBH_4$ (4.5 mg), and stirring continued at 0 °C for 3 h. The reaction was quenched by the addition of saturated NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative HPLC to afford the title compounds as the TFA salts. 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-((1*R*,4*R*)-4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one. 3 mg, R_f = 0.28 (MeOH/DCM, 5/95); ^{1}H NMR (CD_3OD) δ8.97 (s, 1H), 8.30 (s, 1H), 7.80 (d, 1H), 7.66 (dd, 1H), 7.56 (dd, 1H), 7.30 (t, 1H), 7.13 (m, 2H), 6.95 (d, 1H), 5.85 (dd, 1H), 5.11 (dd, 1H), 2.63 (m, 1H), 2.43 (m, 1H), 2.32 (m, 1H), 1.94 (m, 1H); MS (MH^+) 417.0. 2-(6-fluoro-1H-benzo[d]imidazol-1-yl)-9-((1*R*,4*S*)-4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-7H-purin-8(9H)-one. 2 mg, R_f = 0.33 (MeOH/DCM, 5/95); ^{1}H NMR (CD_3OD) δ9.01 (s, 1H), 8.33 (s, 1H), 8.00 (m, 1H), 7.67-6.94 (m, 6H), 5.72 (m, 1H), 4.91 (m, 1H), 2.99 (m, 1H), 2.42-2.05 (m, 3H); MS (MH^+) 417.0.

Jak3 kinase assay

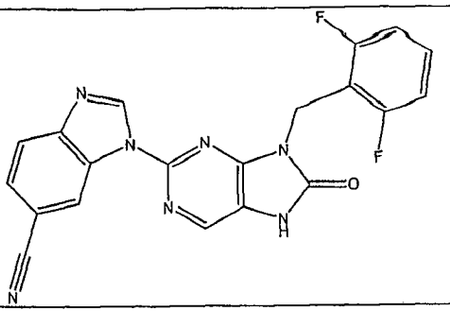
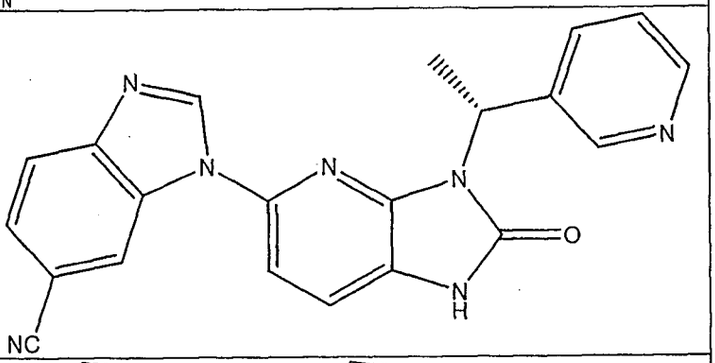
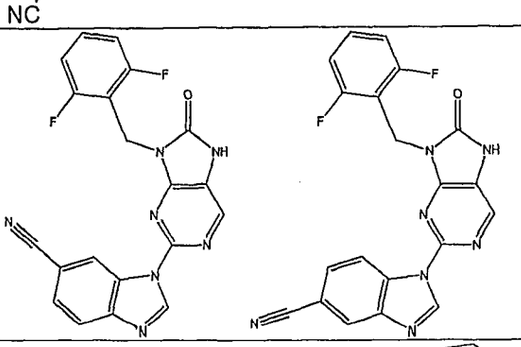
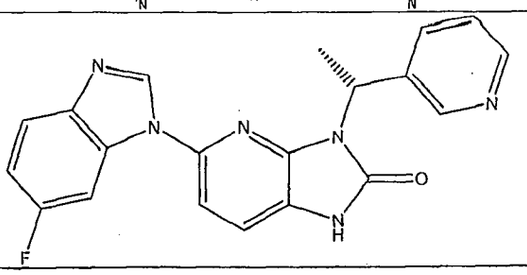
[00395] Human Jak3 cDNA was amplified by PCR. A fragment encoding the catalytic domain of Jak3 (508aa to 1124aa) was ligated with GST at 5' end. This fused GST-Jak3 DNA fragment was cloned into the EcoRI site of the donor plasmid pFastBac 1 (Life Technologies #10359-016). The transformation, transposition, and transfection of insect cells (Sf9) were performed according to the manufacture's instructions. The cell lysate containing recombinant GST-Jak3 was used in the kinase assay. Anti-GST antibody (10 μg/ml, Sigma #G1417) was coated onto a 384-well plate at 4 °C overnight. Cell lysate containing GST-Jak3 (1:100 dilution) was added to the anti-GST coated plates, and GST-Jak3 was captured by immobilized anti-GST antibody. Testing compounds and substrate mix (50 mM HEPES, pH 7, 0.5 mM Na_3VO_4, 25 mM $MgCl_2$, 1 mM DTT, 0.005% BSA, 1 μM ATP, and 4.5 μg/ml

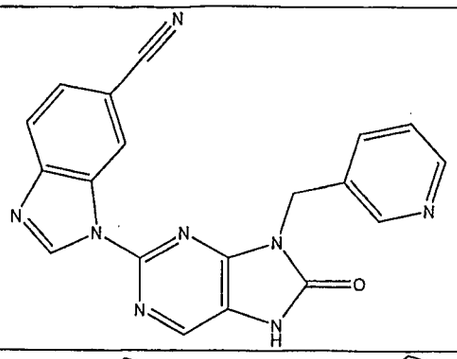
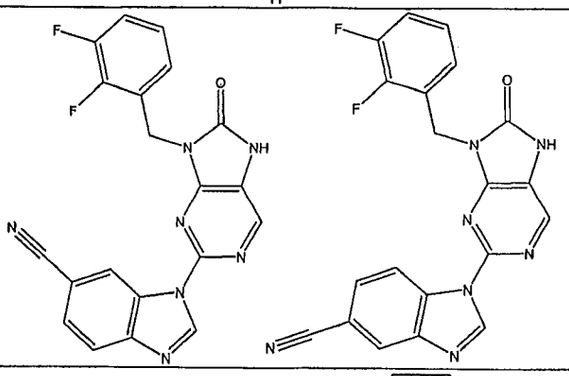
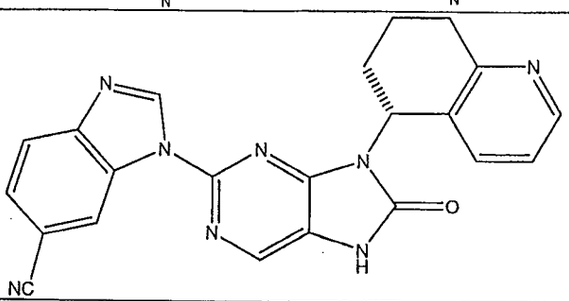
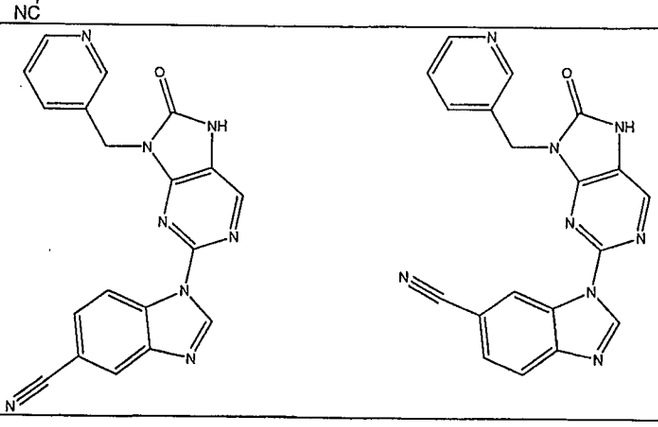
biotinyl poly-Glu,Ala,Tyr) were added to the plate to initiate the reaction. After a 60-min incubation, the reaction was stopped by 4 mM EDTA, and phosphorylation of biotinyl poly-Glu,Ala,Tyr was detected using 17 μg/ml Cy5-streptavidin (Amersham, #PA92005) and 2.7 μg/ml Europium-conjugated anti-phosphotyrosine antibody (PerkinElmer #AD0069) using homogeneous time-resolved fluorescence (HTRF) technology.

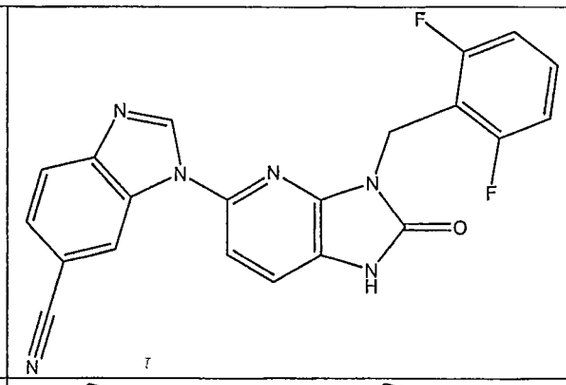
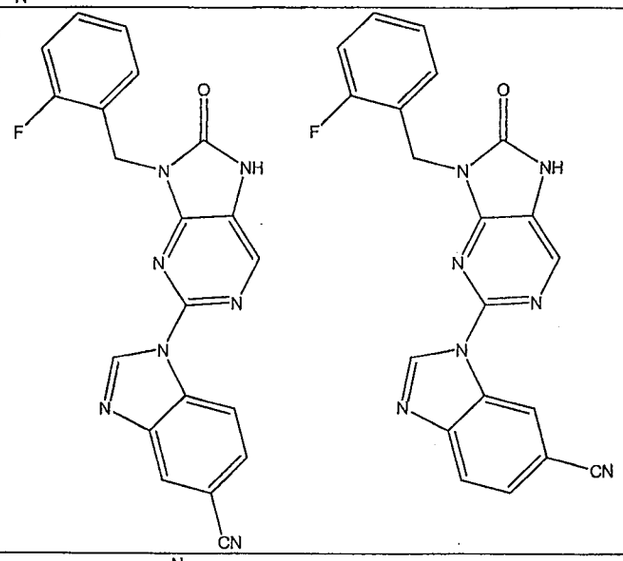
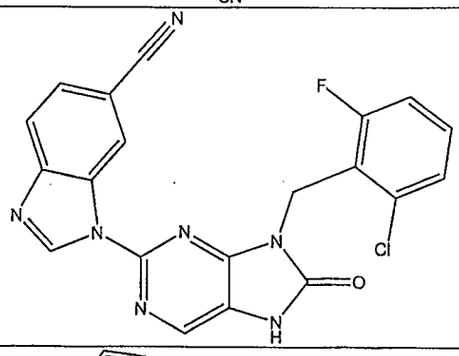
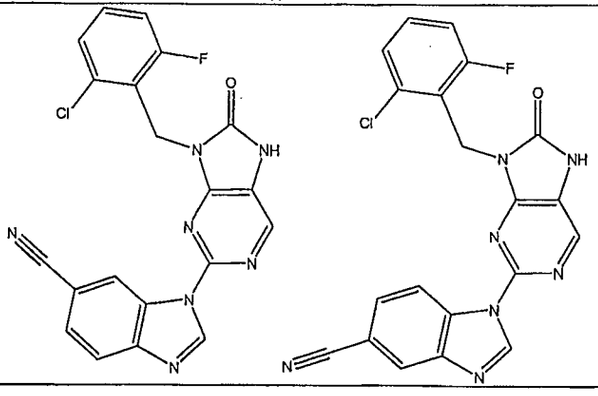
Jak3 cellular assay

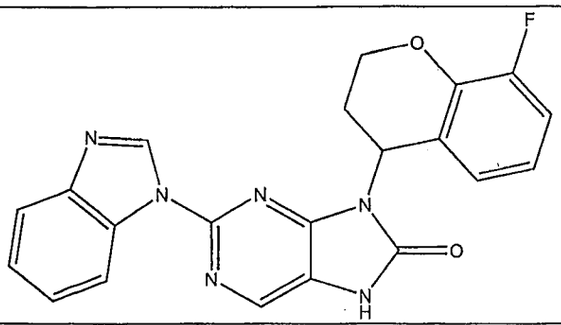
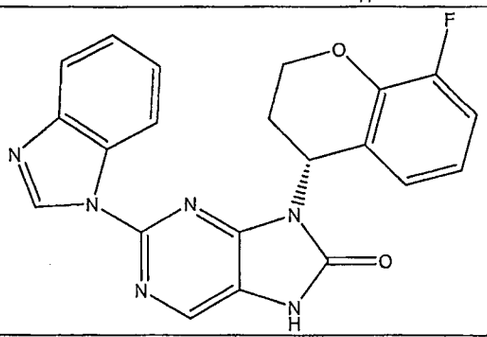
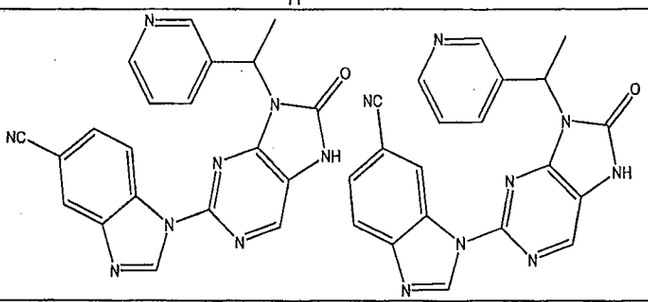
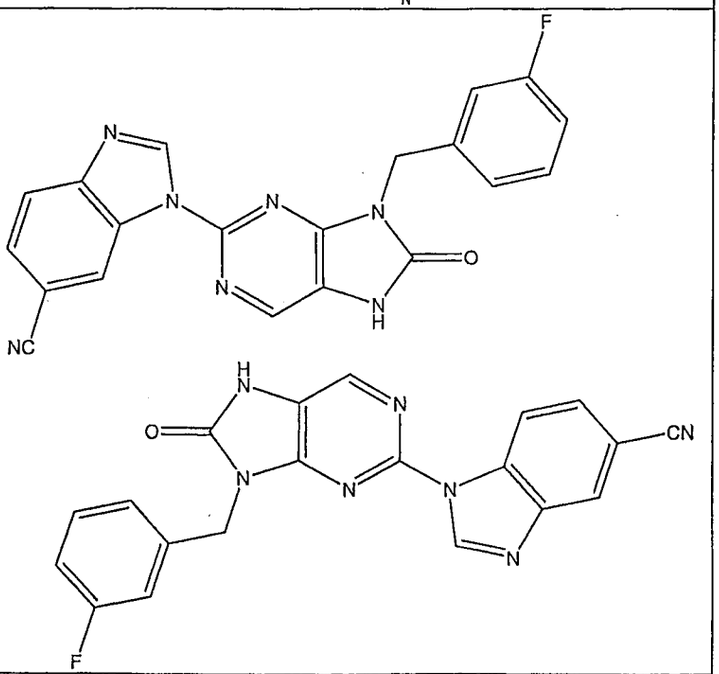
[00396] The mouse F7 pre-B lymphocyte cell line was used for the cellular Jak3 assay. Human IL-2Rβc cDNA is stably expressed in F7 cells (Kawahara et al., 1995). F7 cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum plus IL-3. Cells (30,000 cells/well) in serum-free medium were seeded in 96-well plates for the cell proliferation assay. Testing compounds were added to cells, followed by the addition of IL-2 (final 20 ng/ml). After a 24-h incubation, the number of viable cells was determined by the CellTiter-Glo Luminescent Cell Viability Assay kit (Promega, #G7573) according to the manufacturer's instructions.

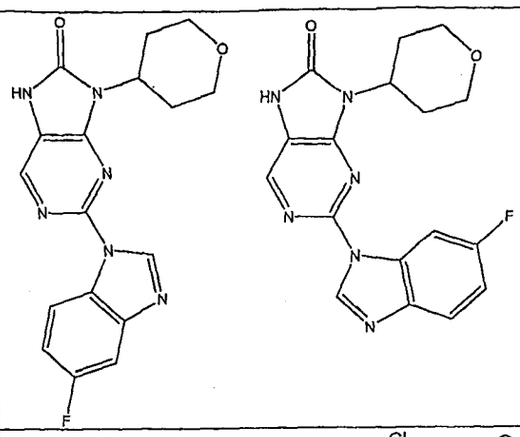
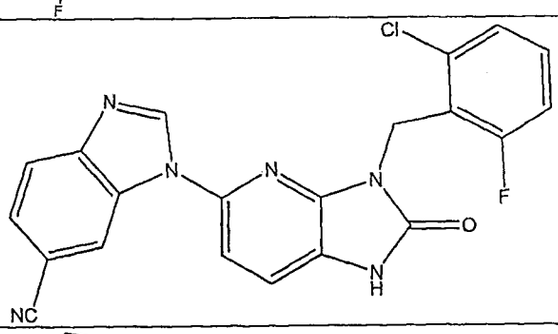
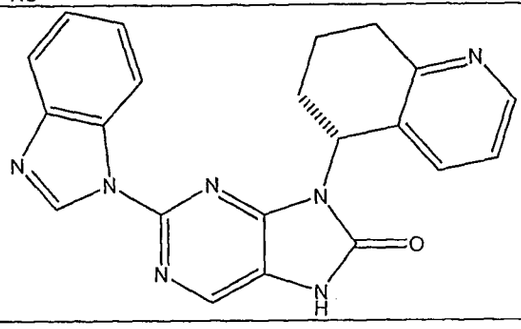
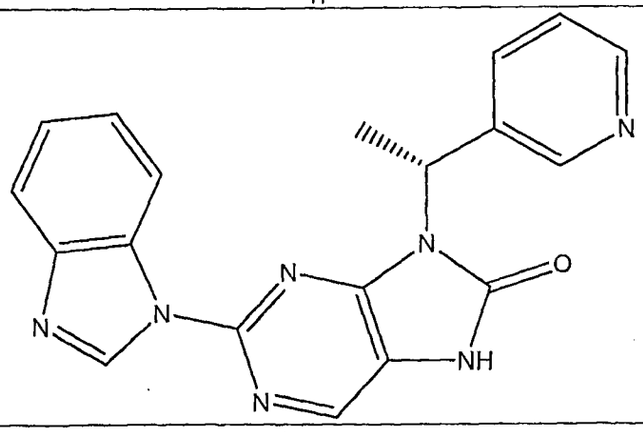
[00397] The results of testing of representative species are shown below. The compounds in Table 1 exhibited IC_{50} less than 100nM. The compounds in Table 2 exhibited IC_{50} between 101 nM and 1μM. The compounds in Table 3 exhibited IC_{50} between 1μM and 10μM.

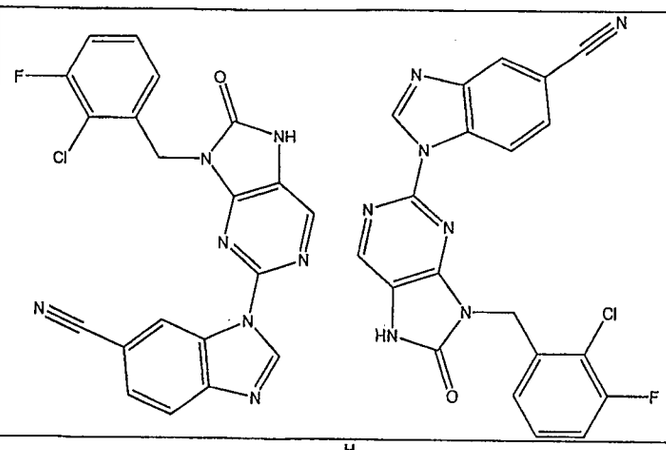
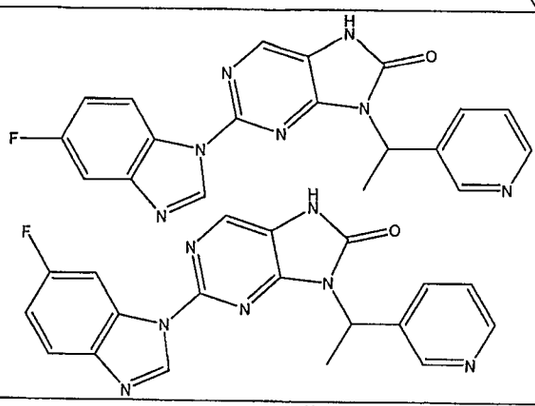
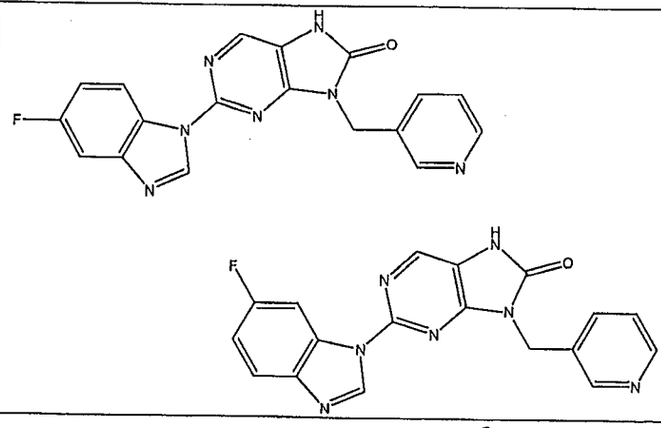
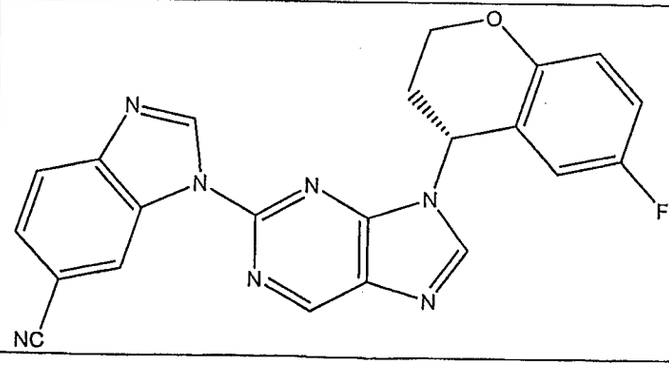
Synthesis Example	Reference No.	TABLE 1
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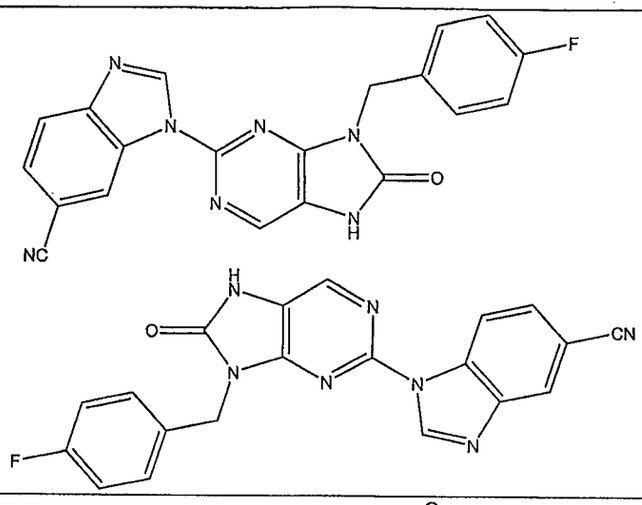
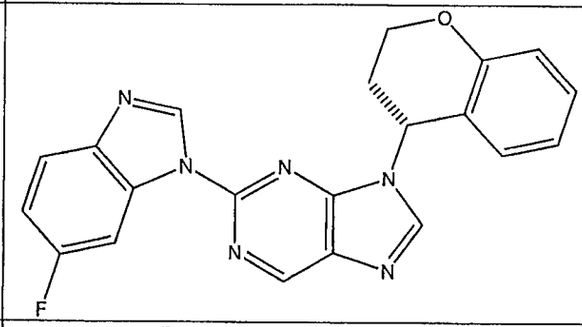
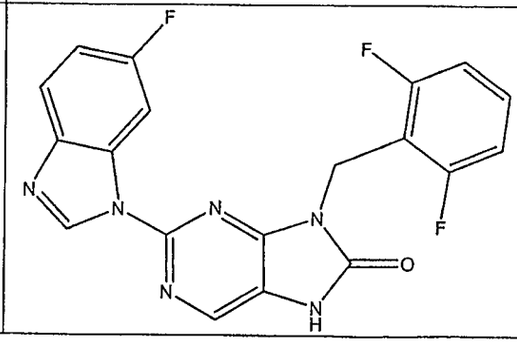
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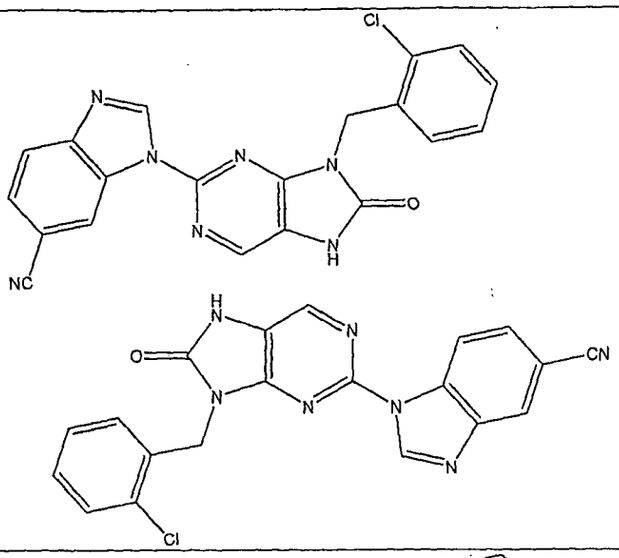
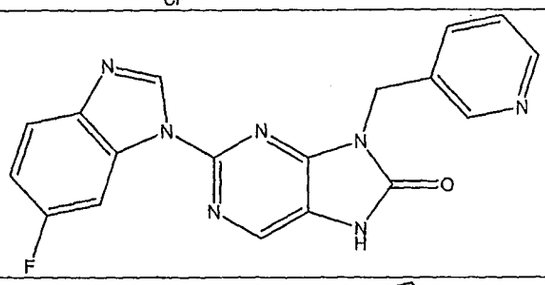
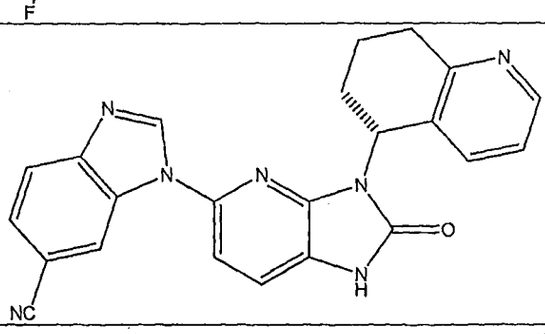
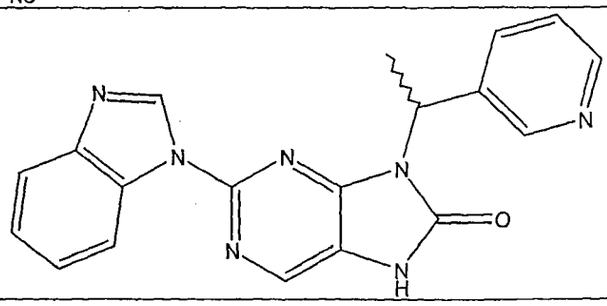
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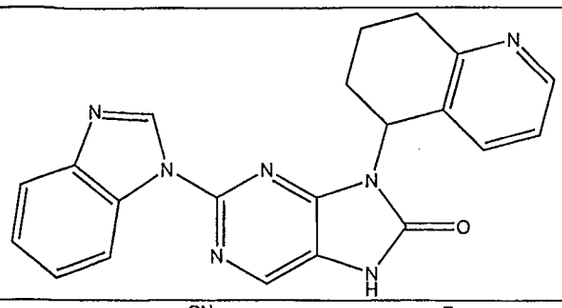
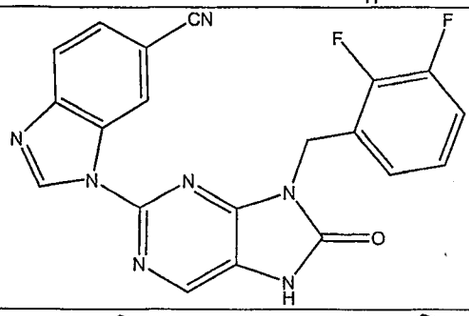
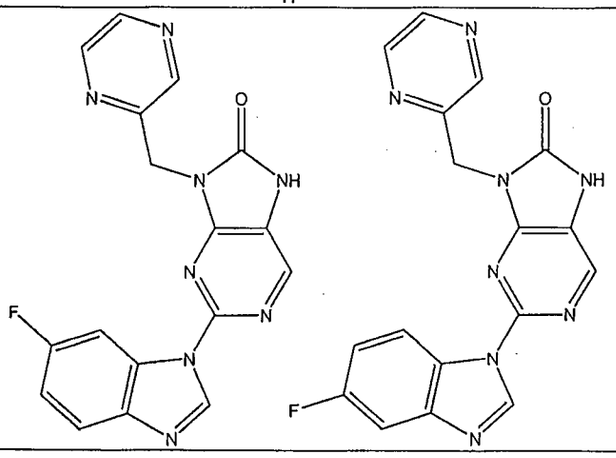
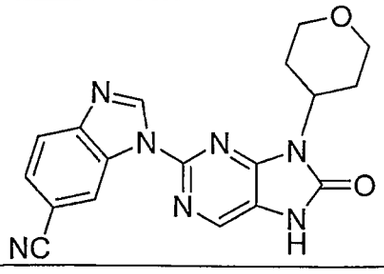
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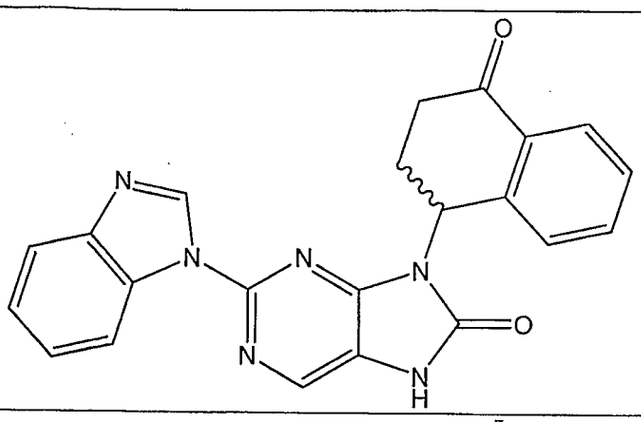
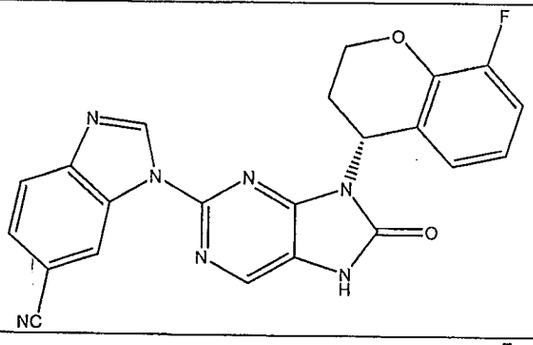
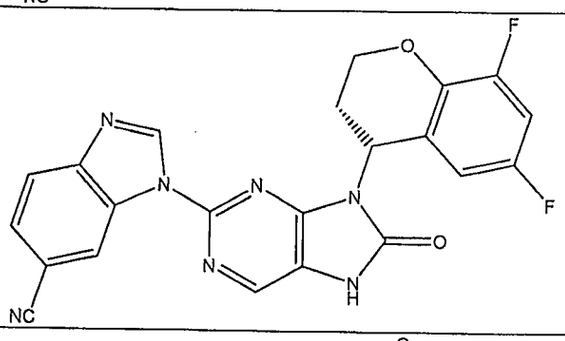
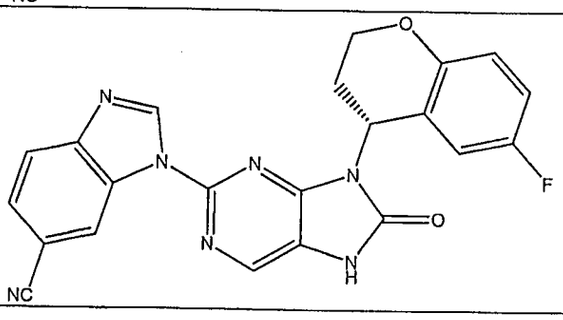
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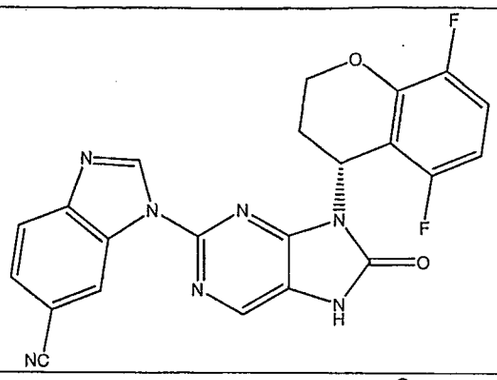
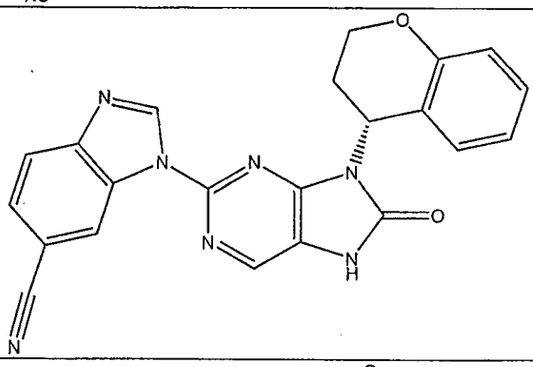
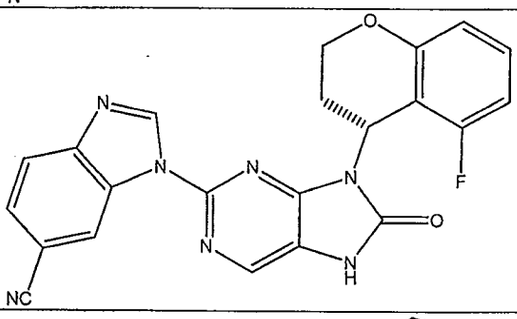
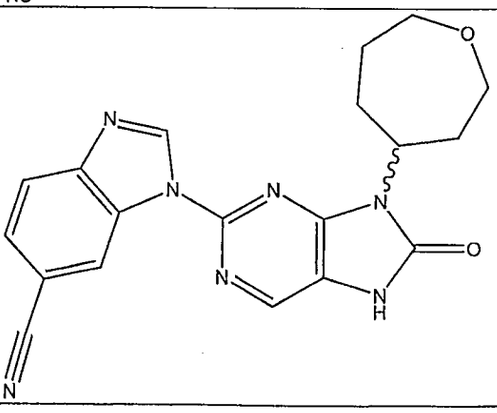
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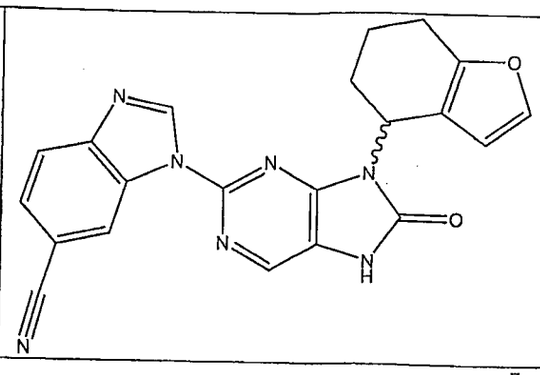
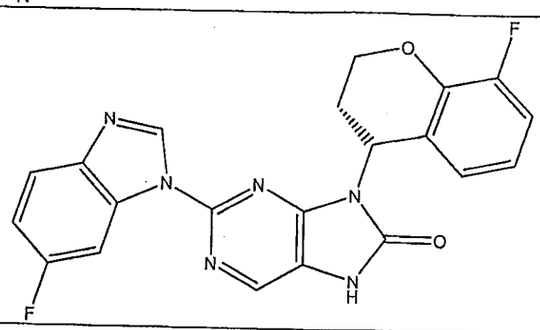
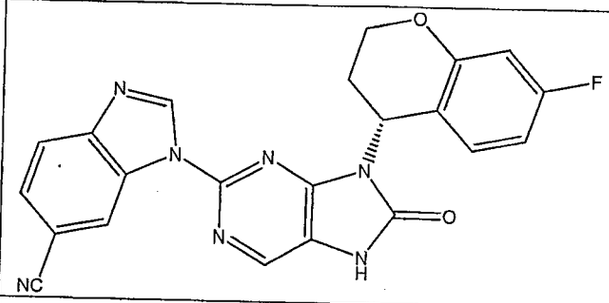
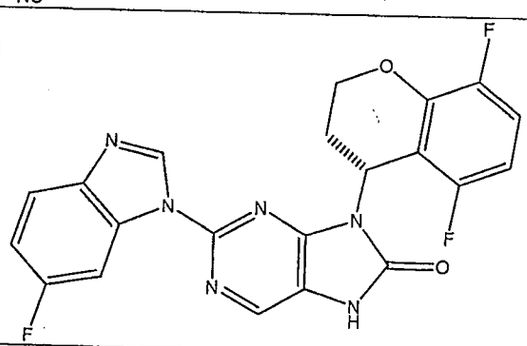
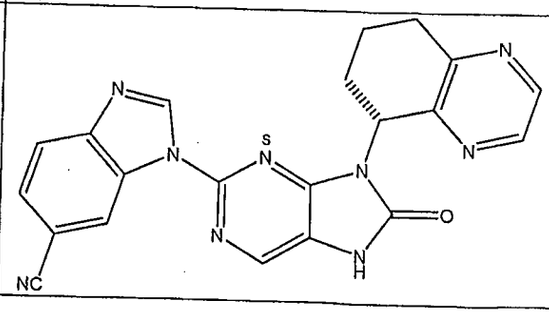
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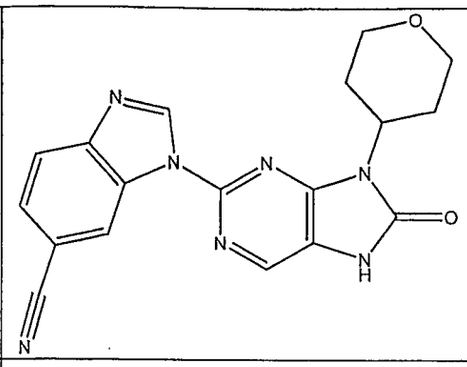
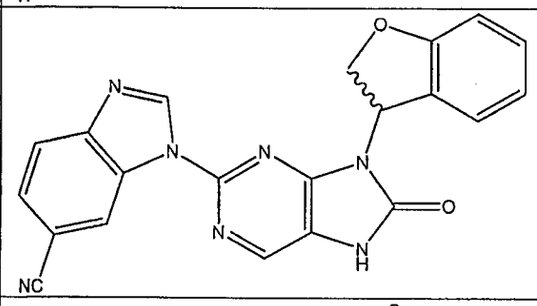
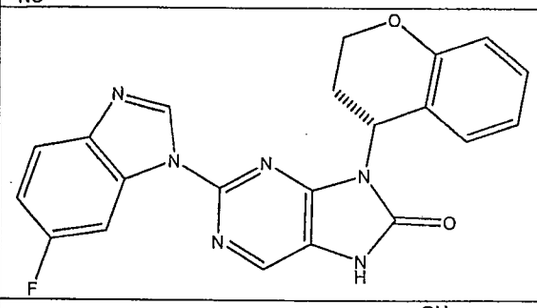
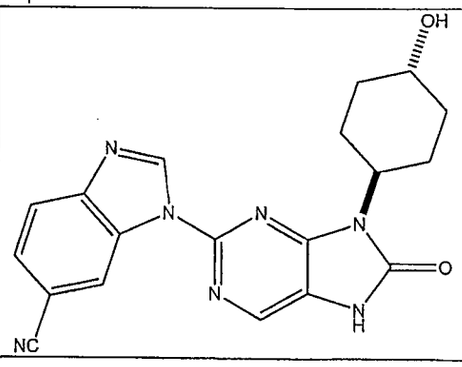
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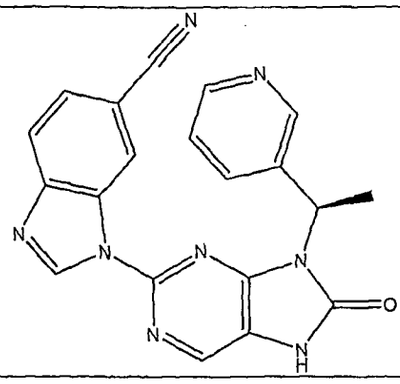
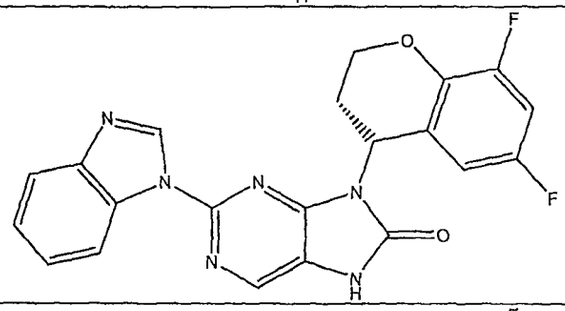
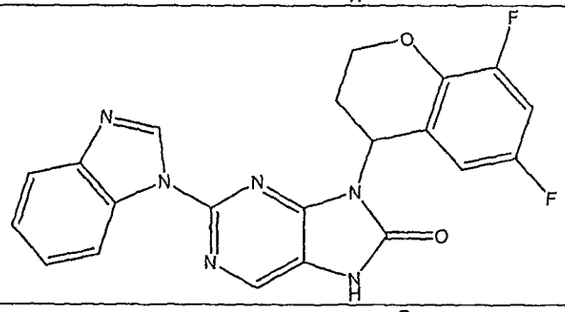
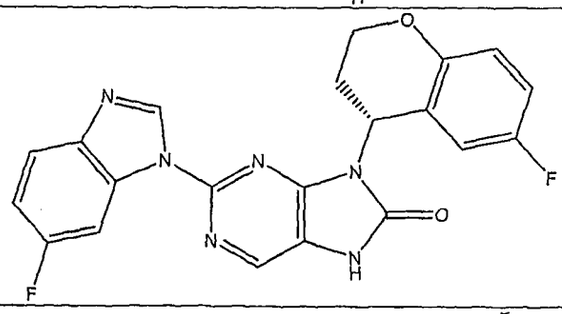
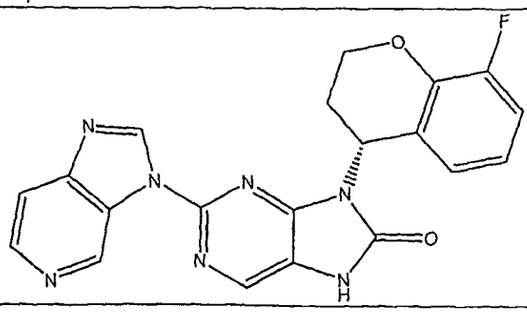
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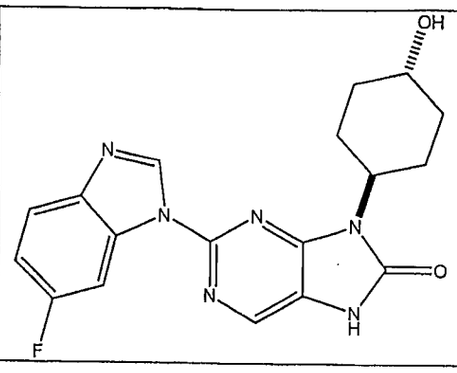
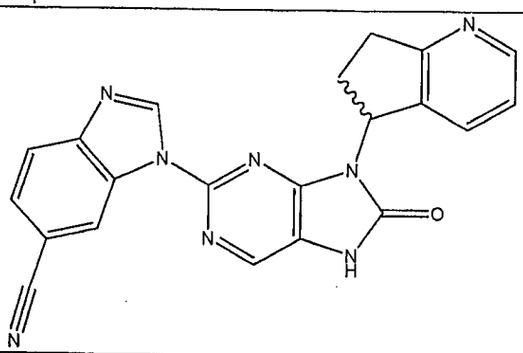
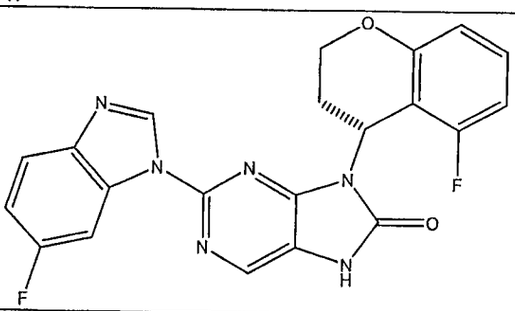
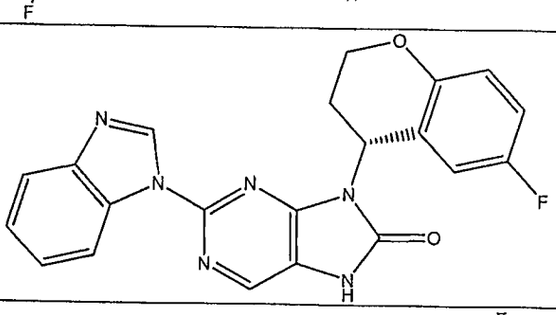
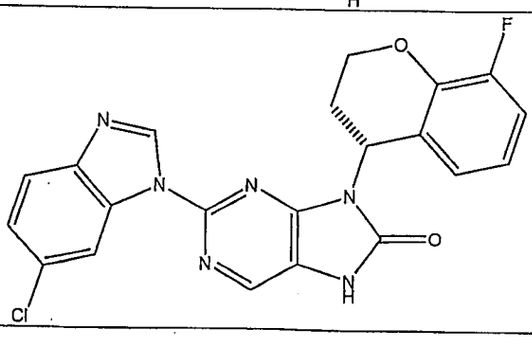
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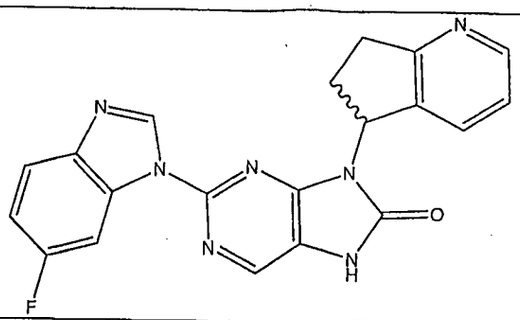
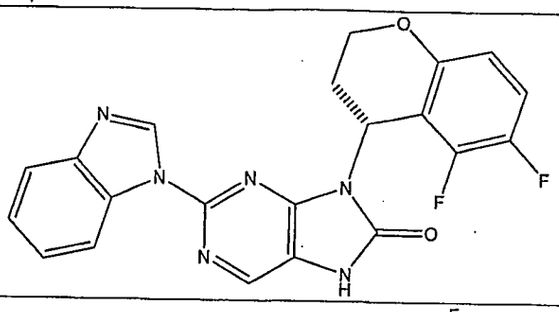
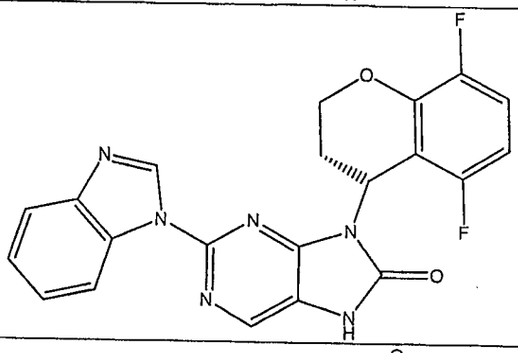
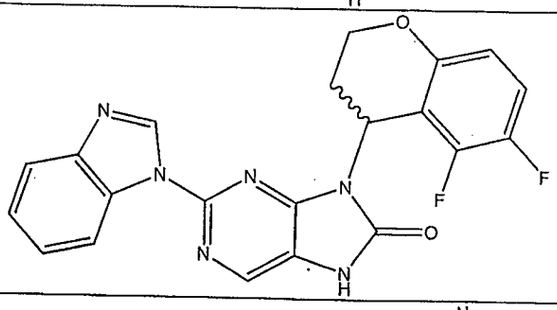
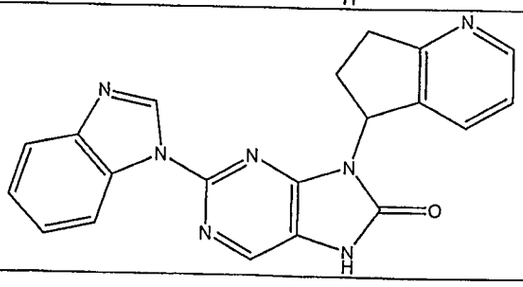
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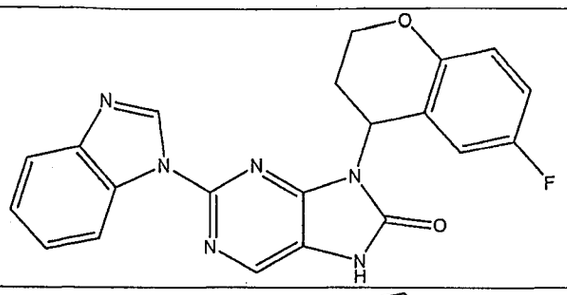
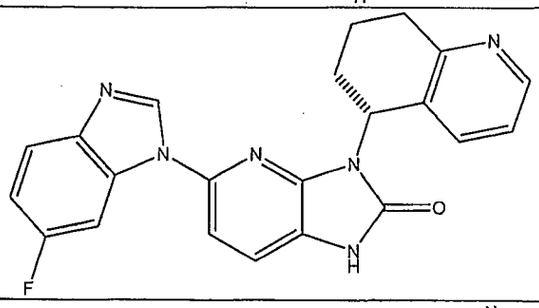
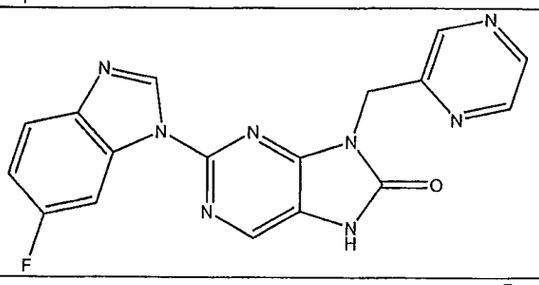
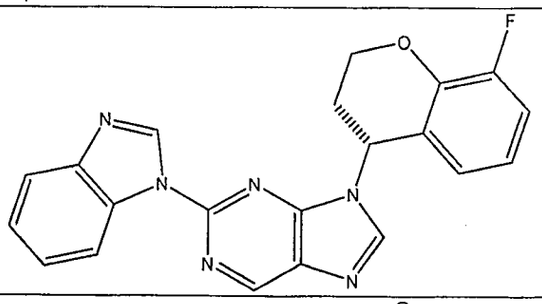
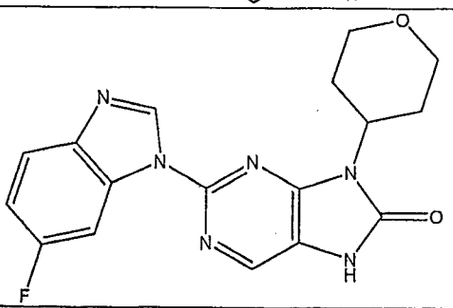
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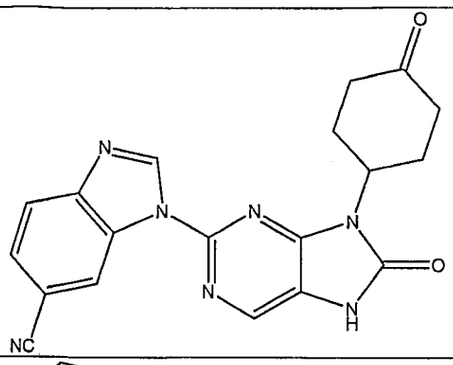
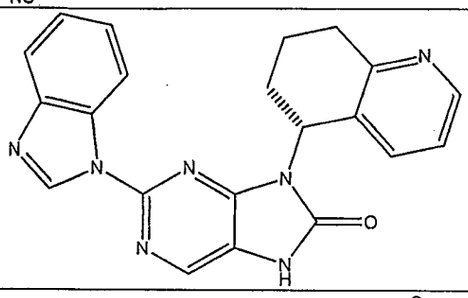
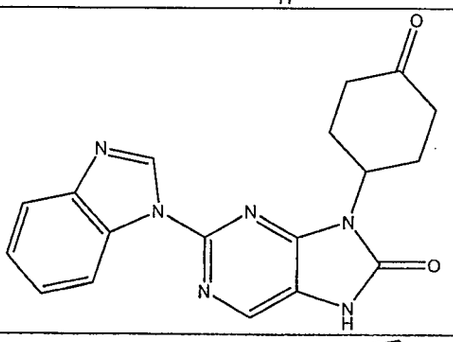
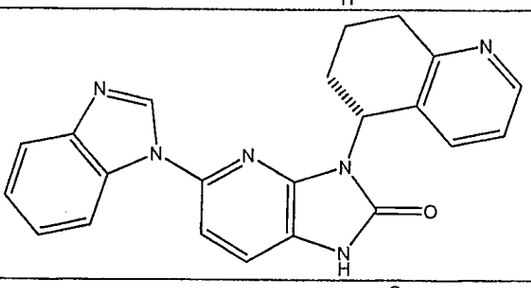
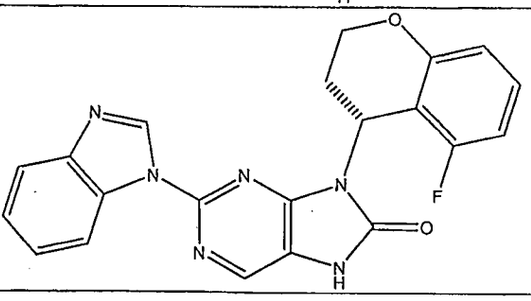
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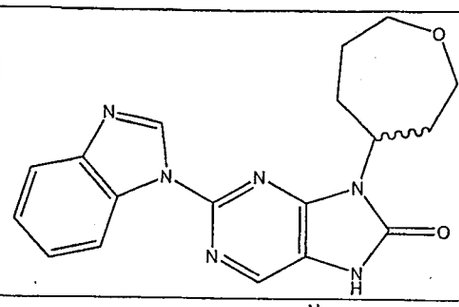
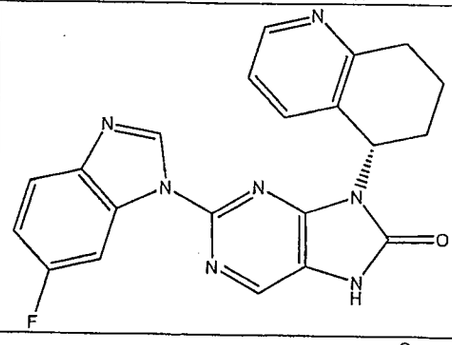
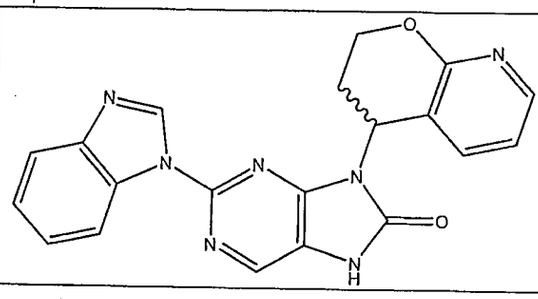
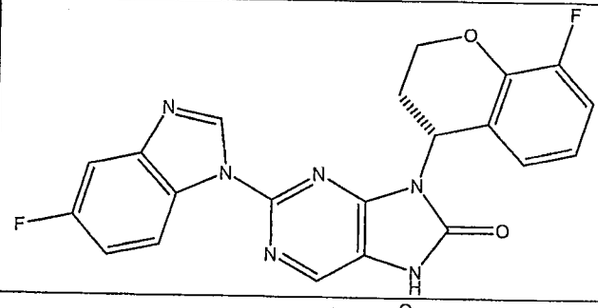
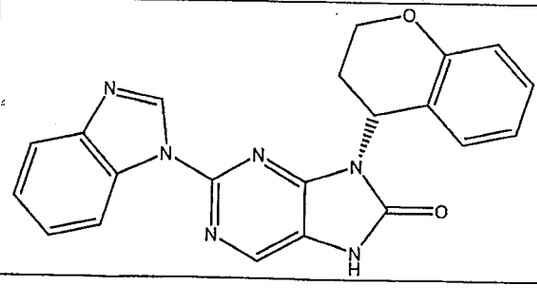
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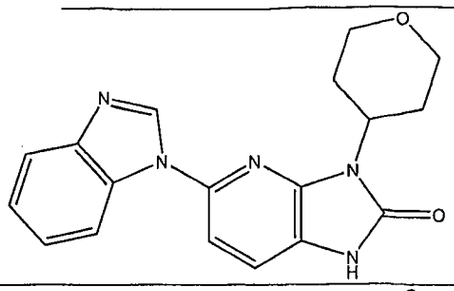
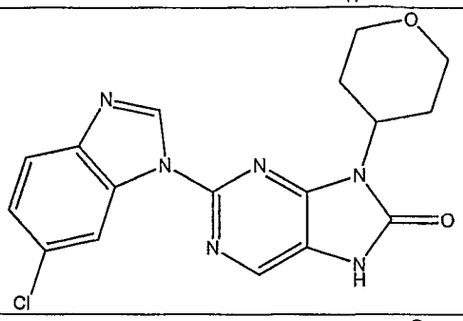
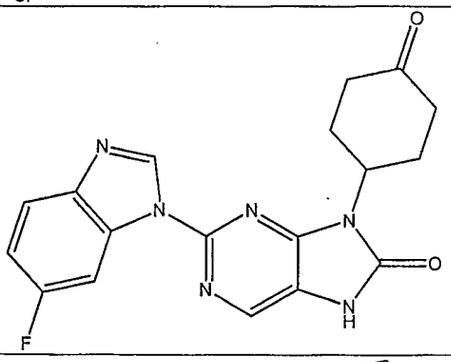
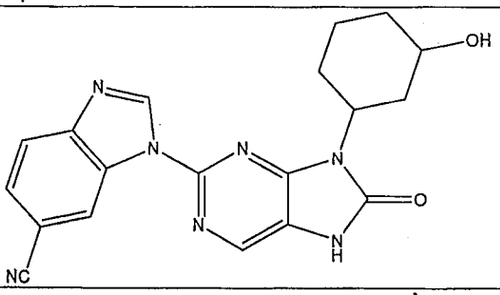
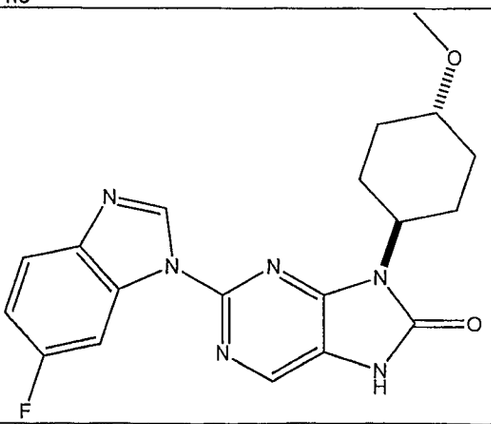
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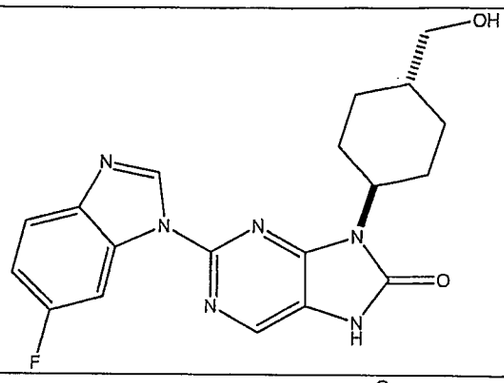
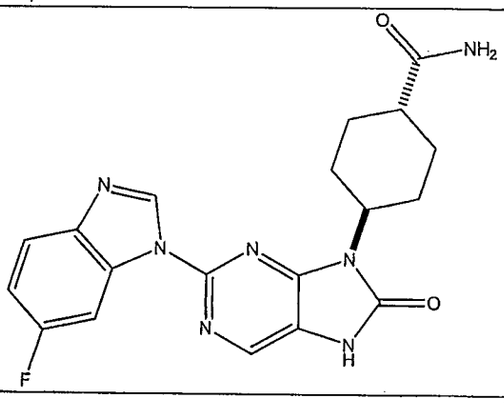
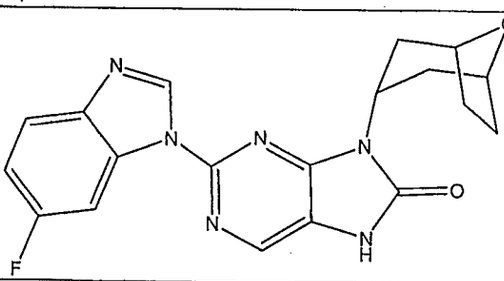
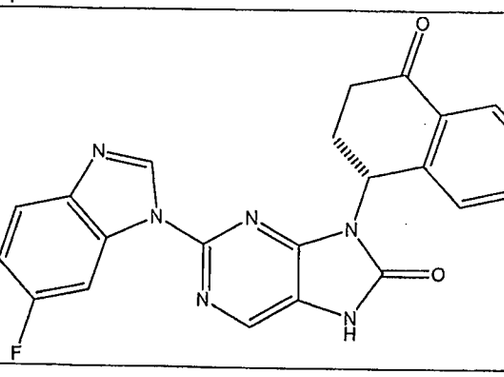
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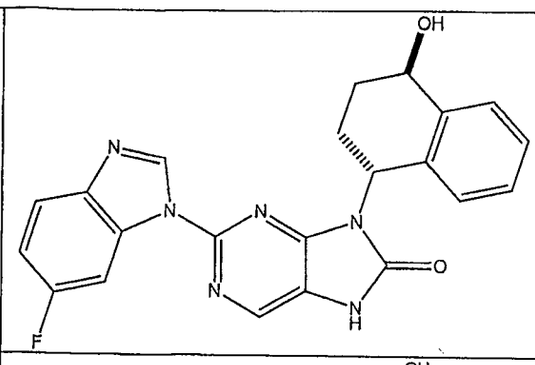
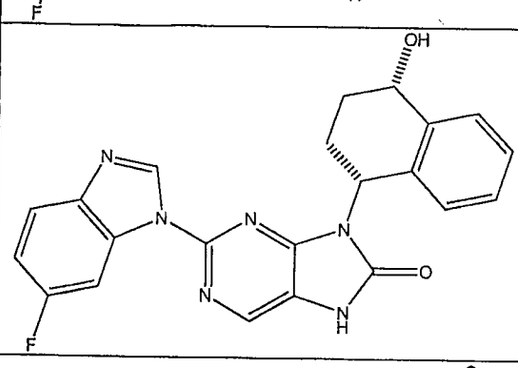
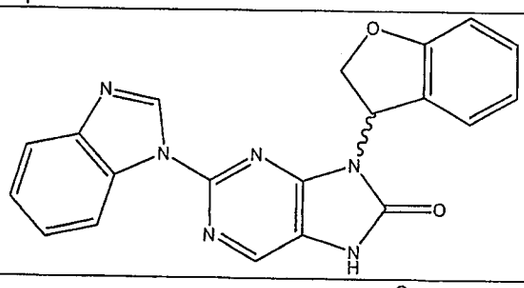
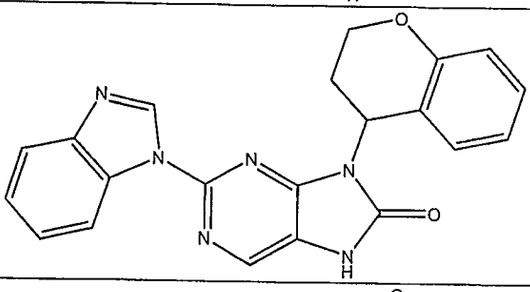
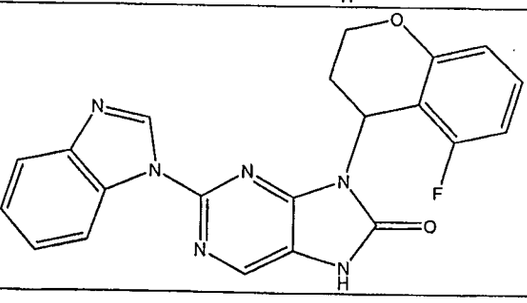
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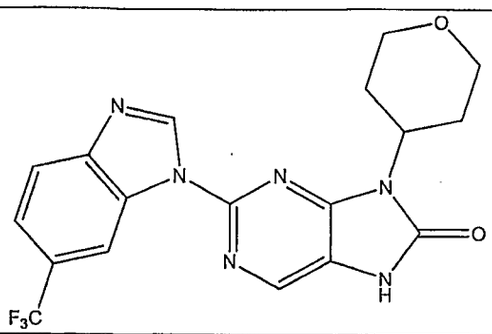
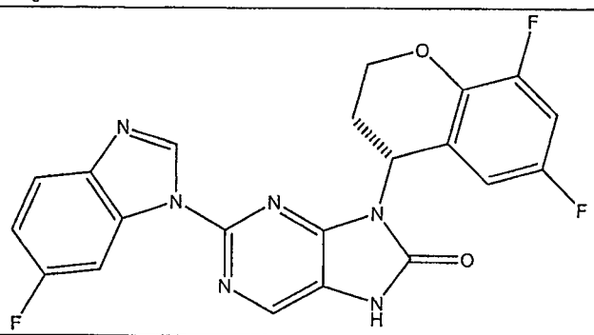
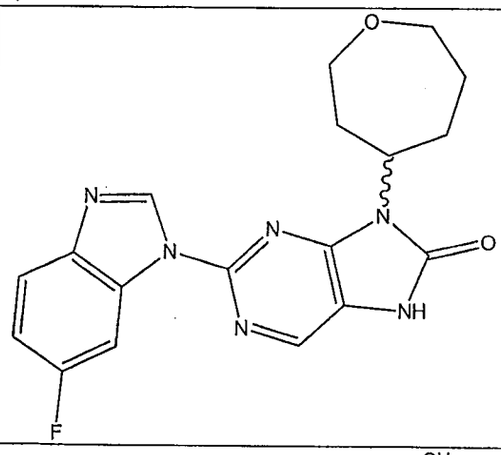
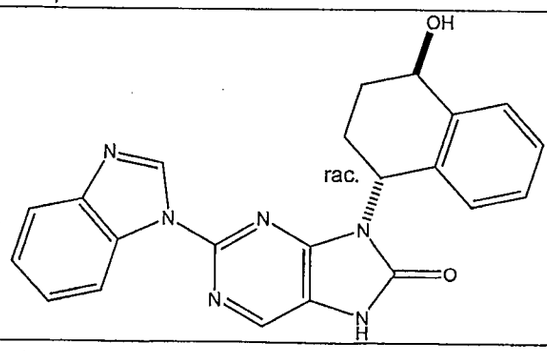
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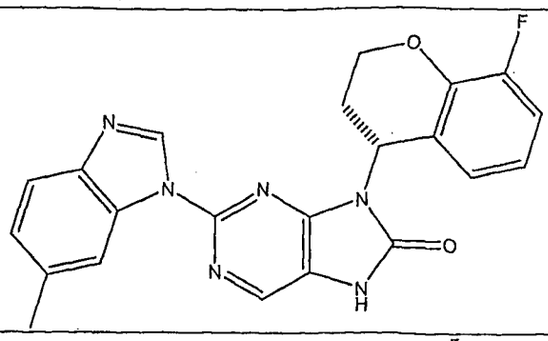
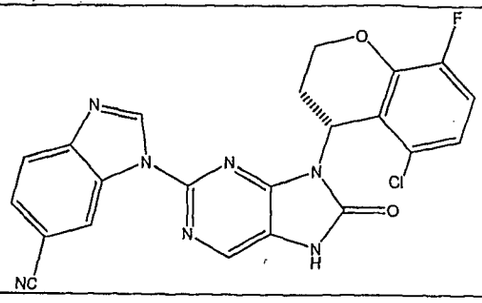
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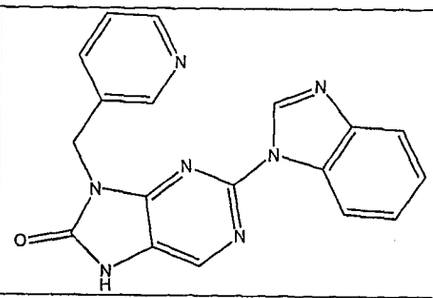
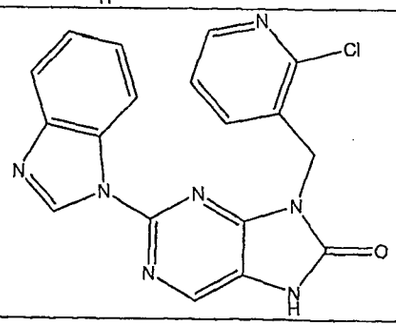
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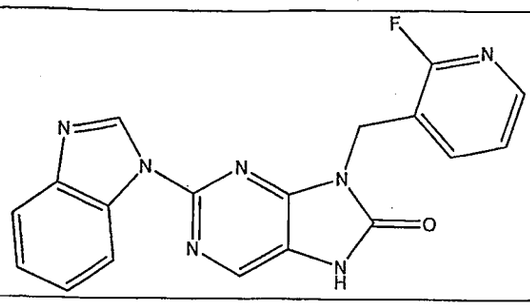
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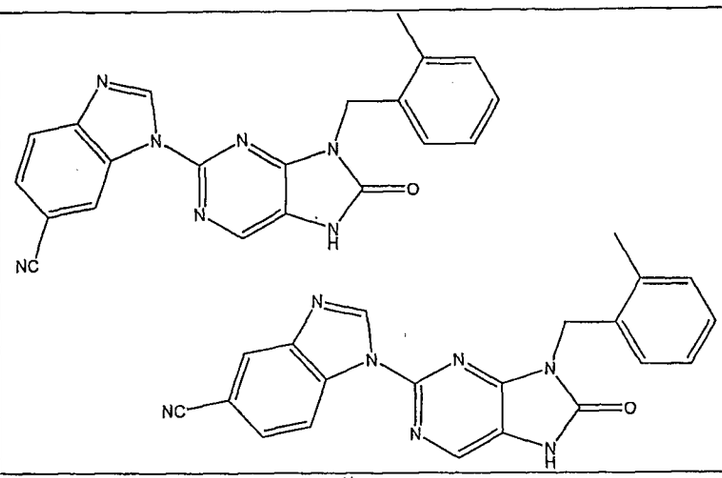
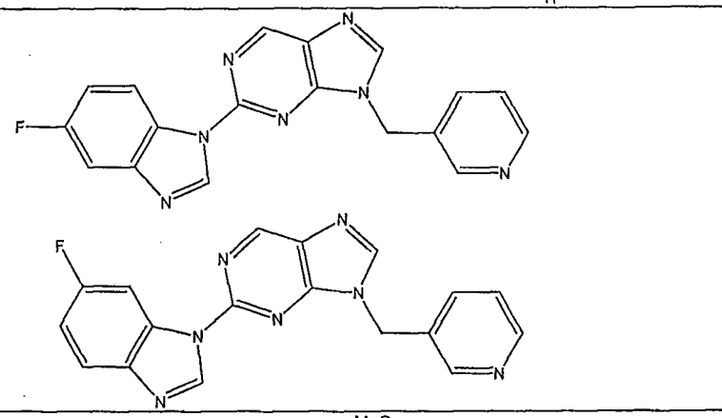
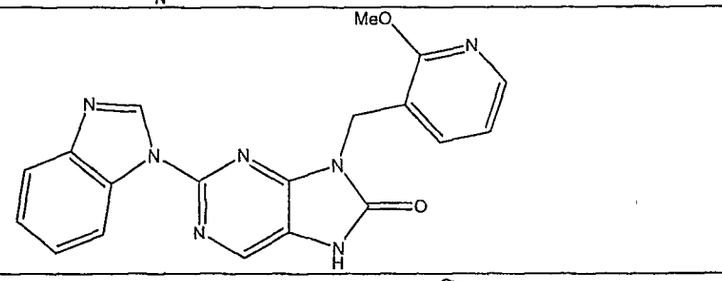
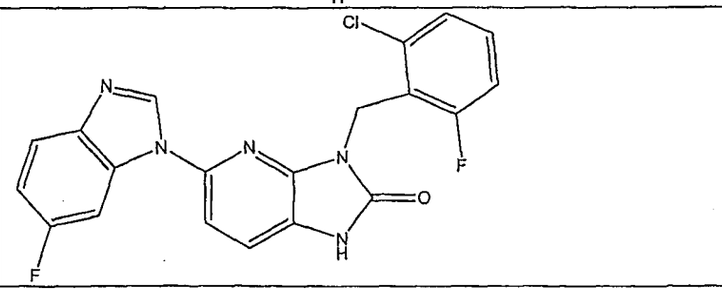
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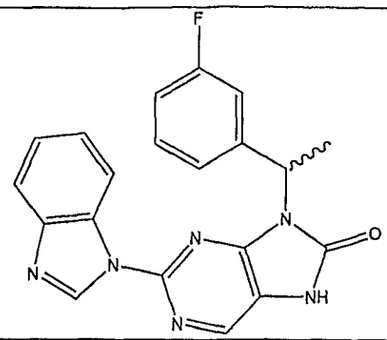
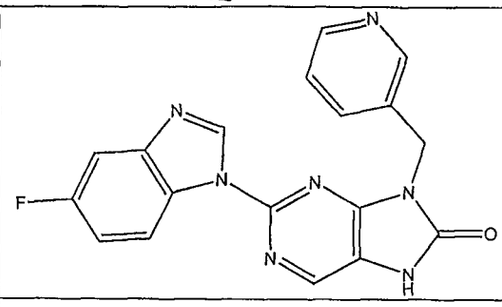
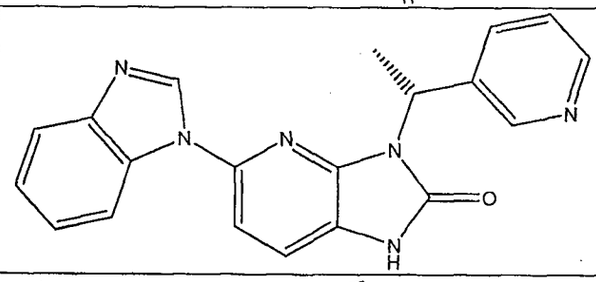
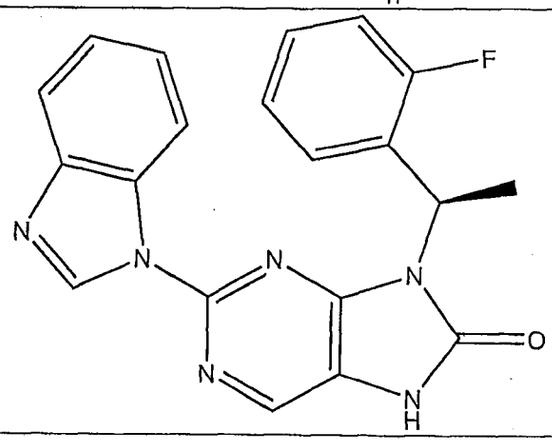
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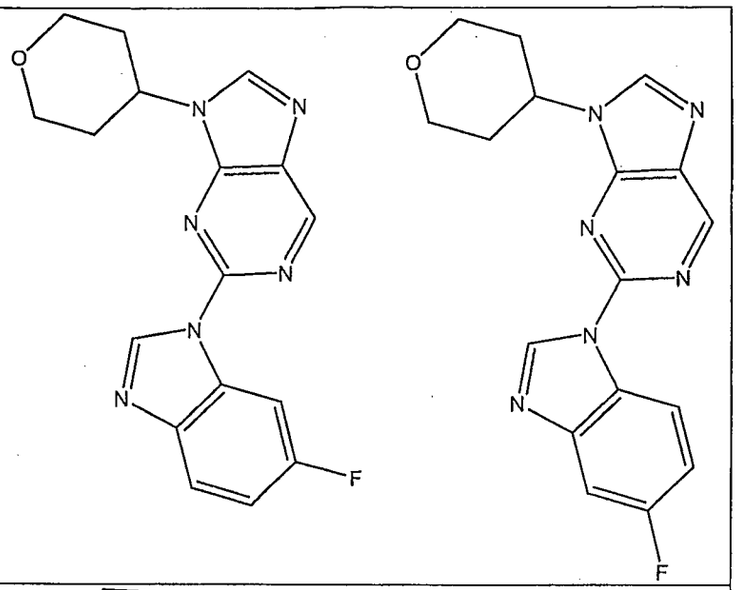
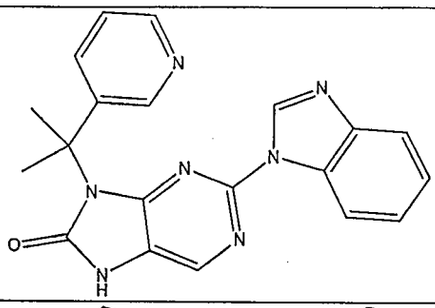
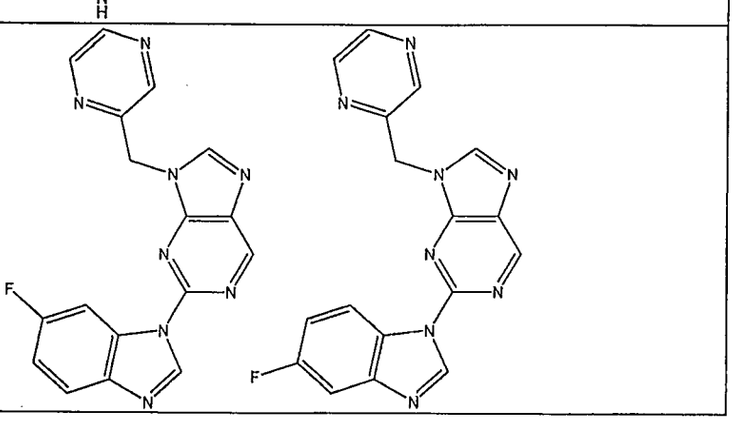
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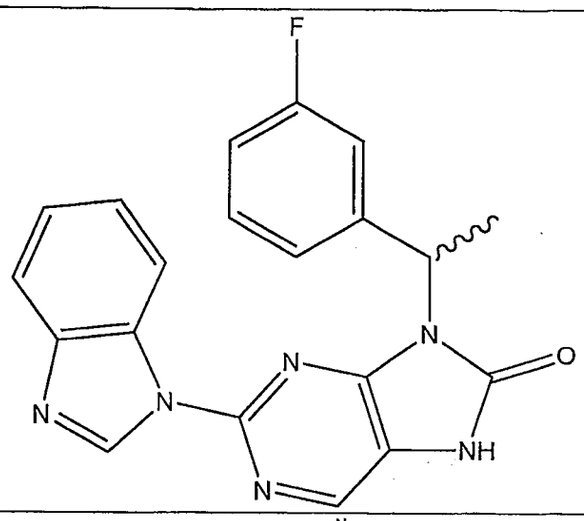
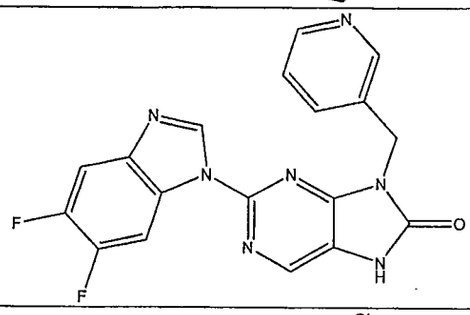
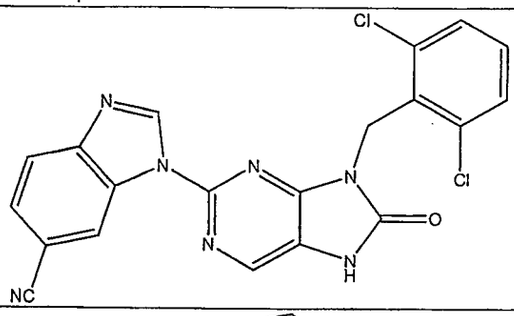
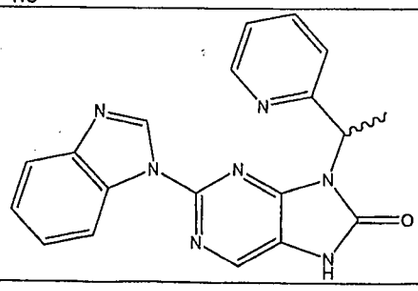
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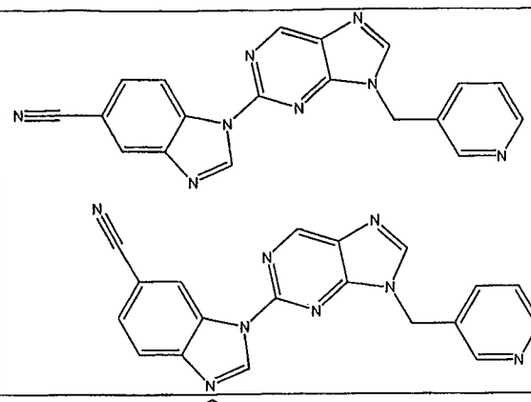
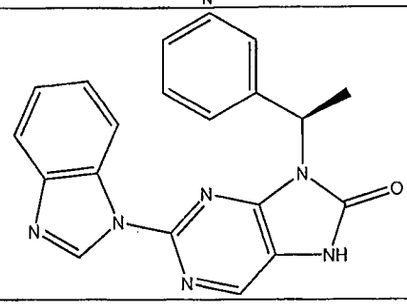
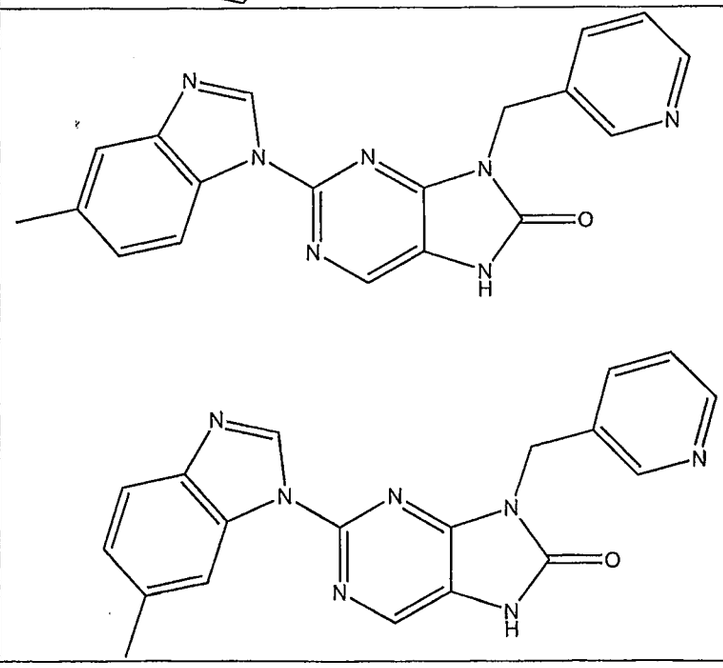
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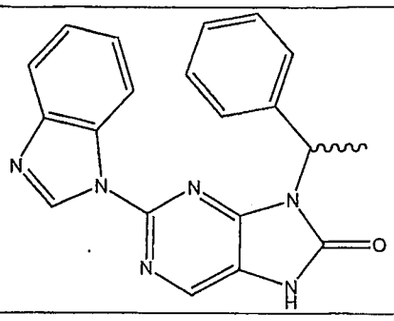
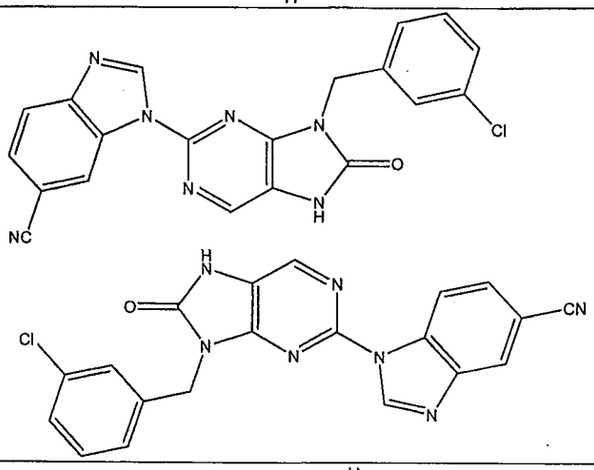
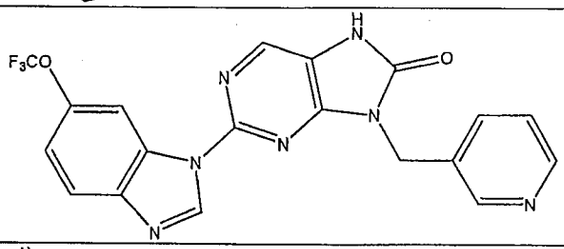
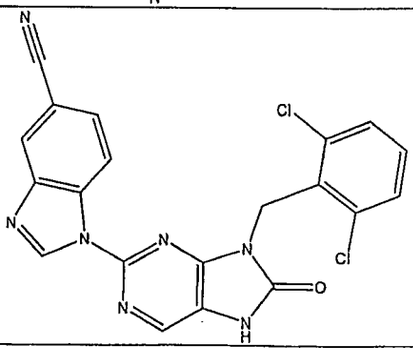
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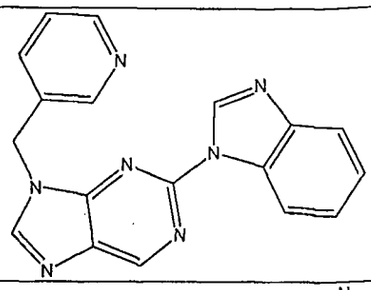
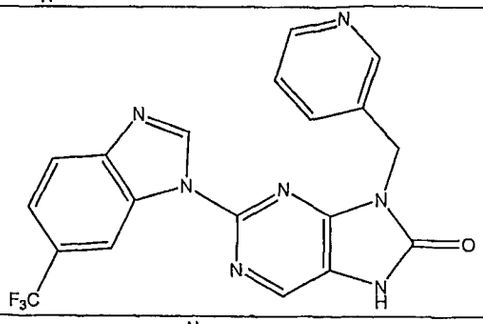
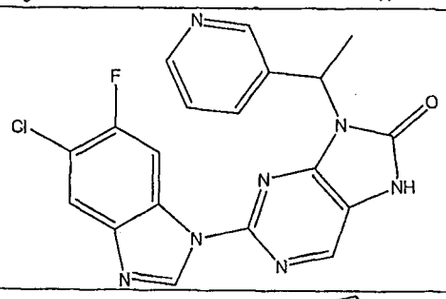
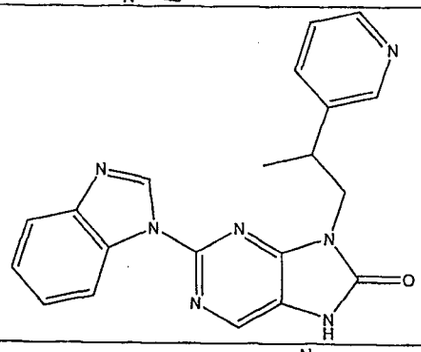
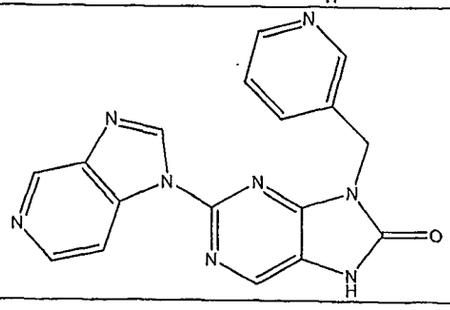
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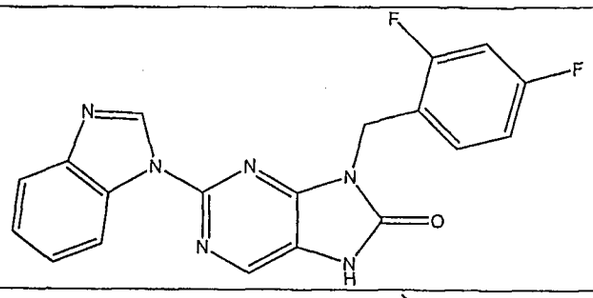
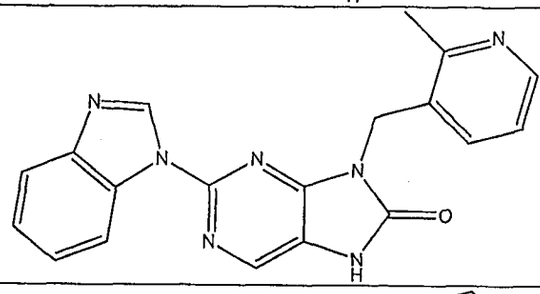
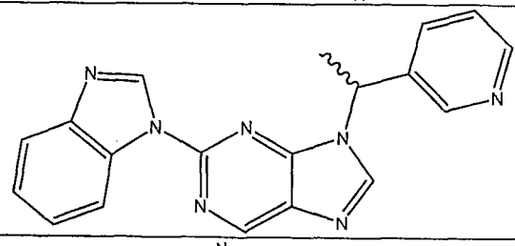
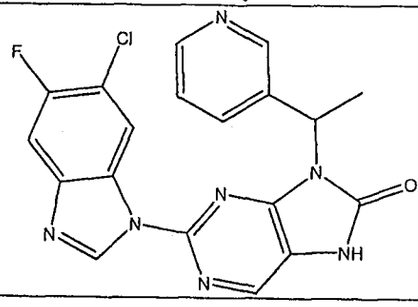
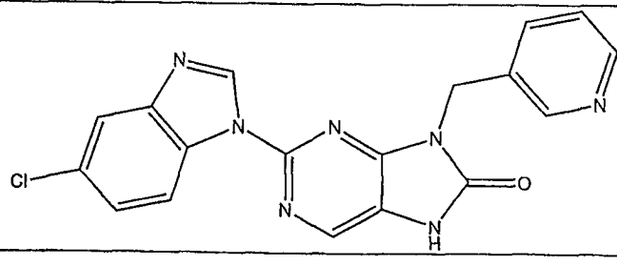
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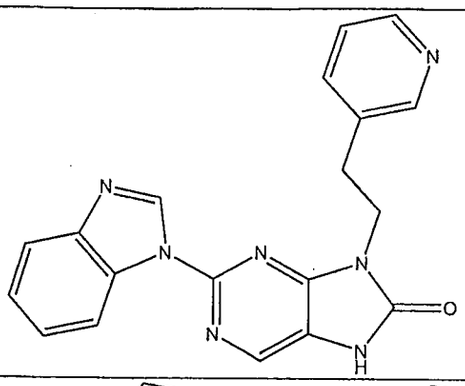
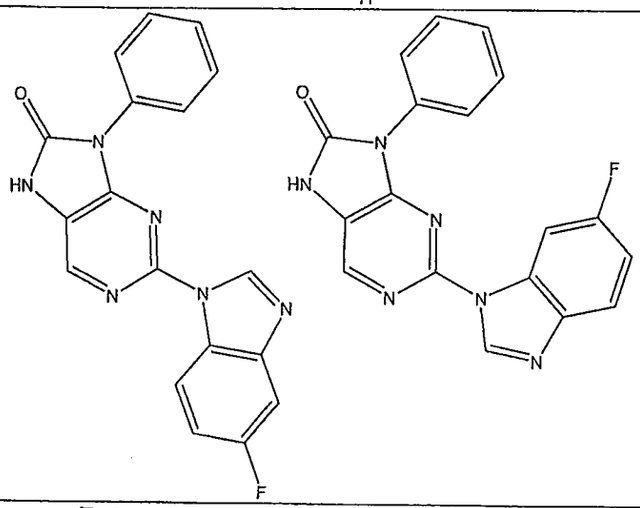
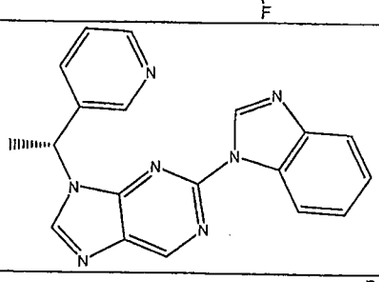
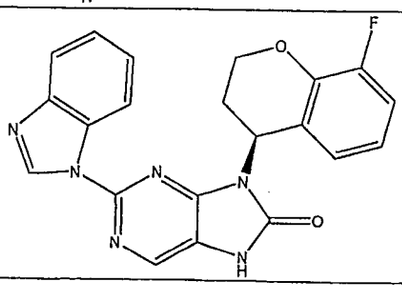
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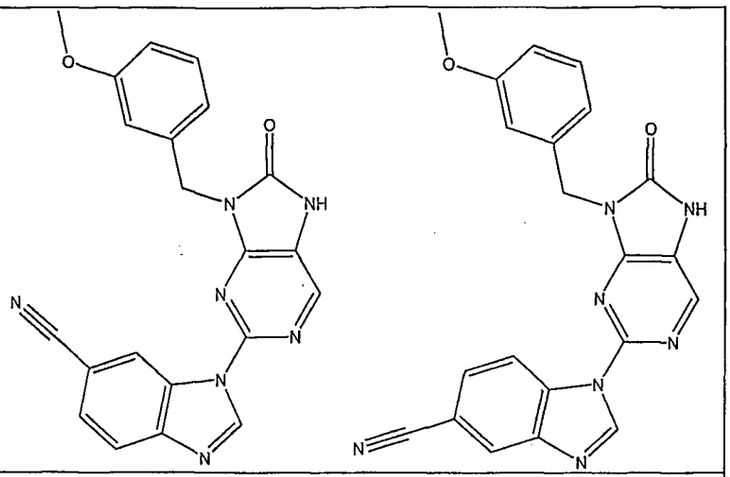
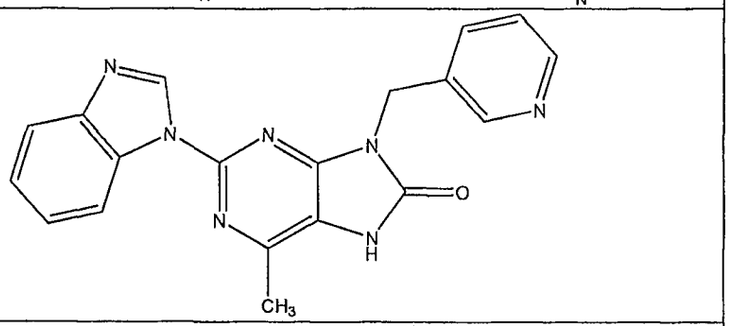
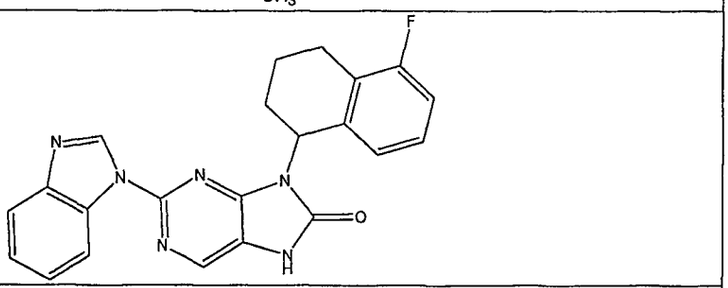
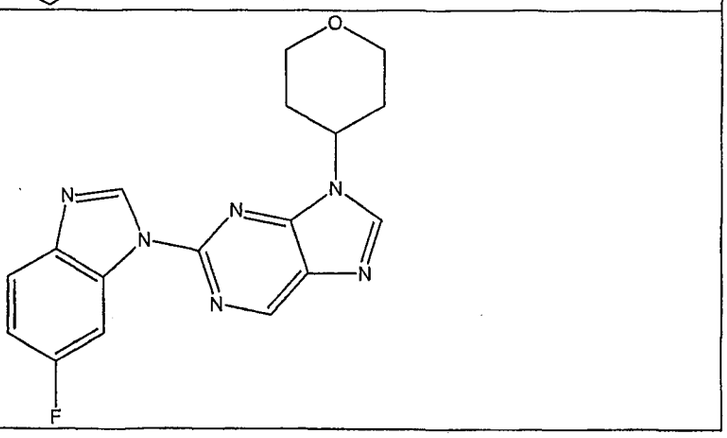
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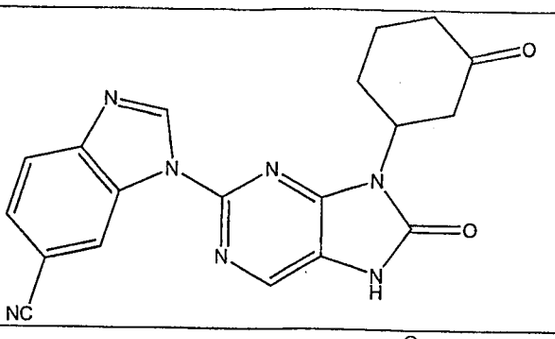
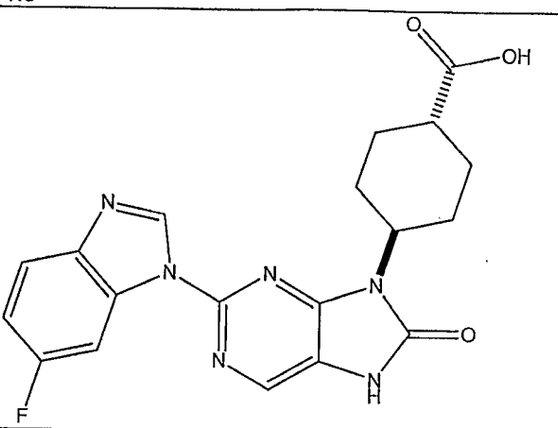
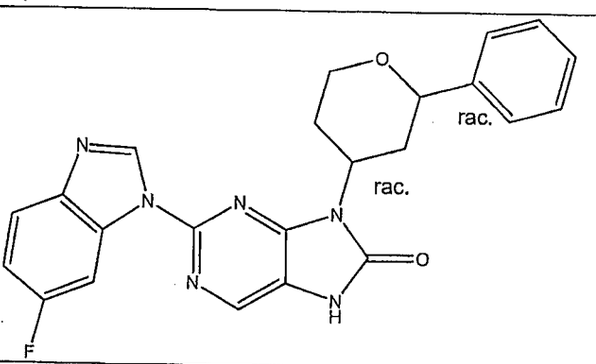
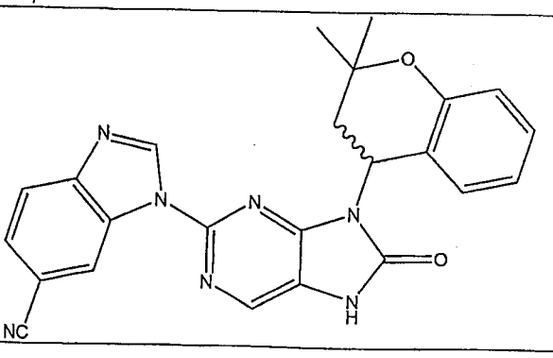
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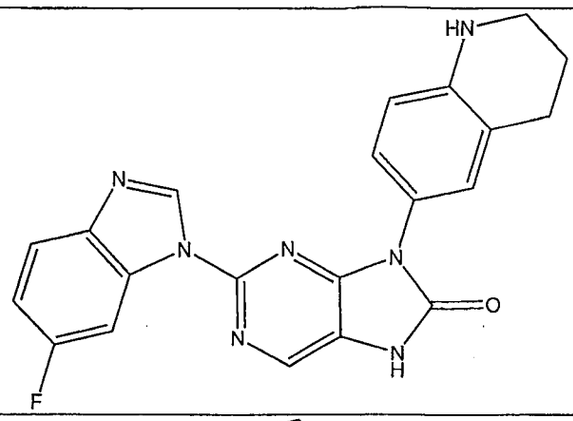
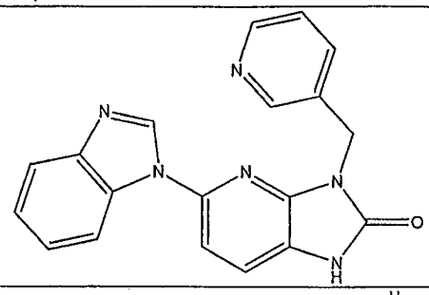
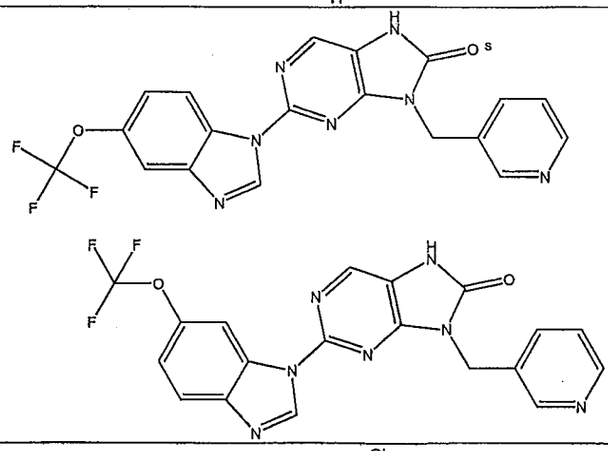
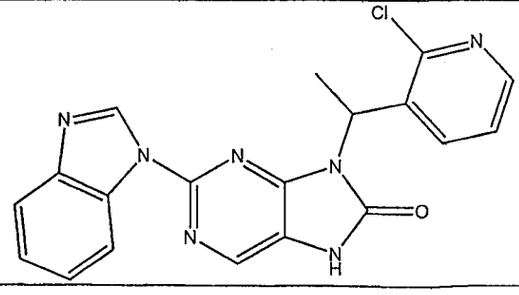
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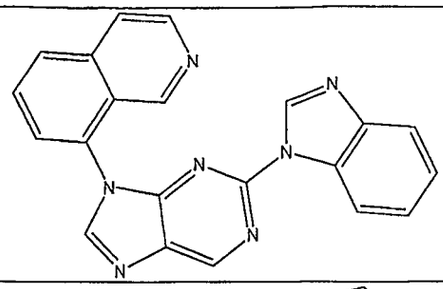
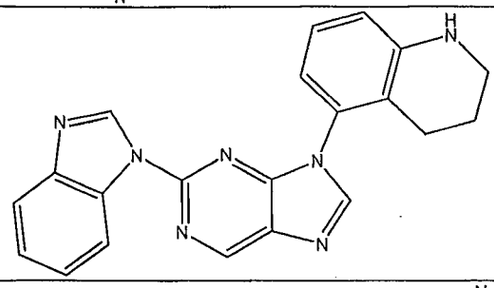
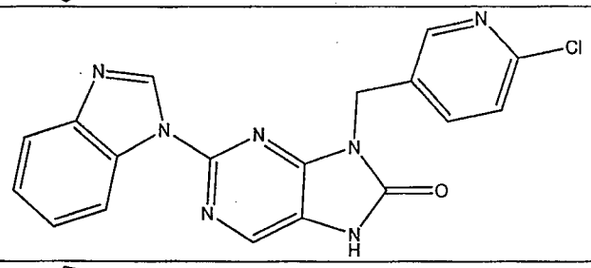
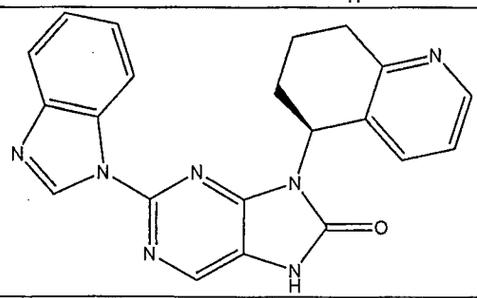
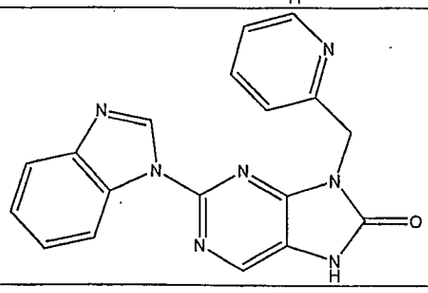
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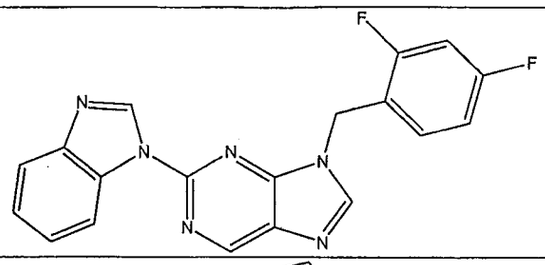
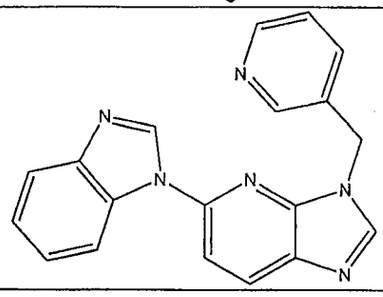
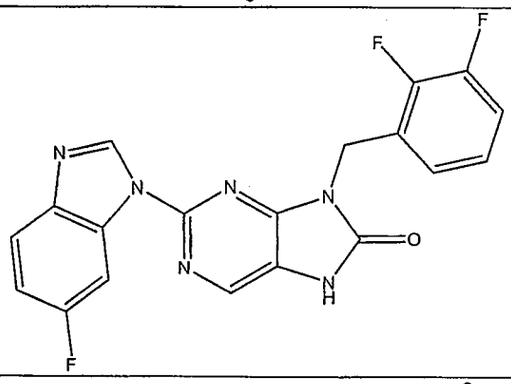
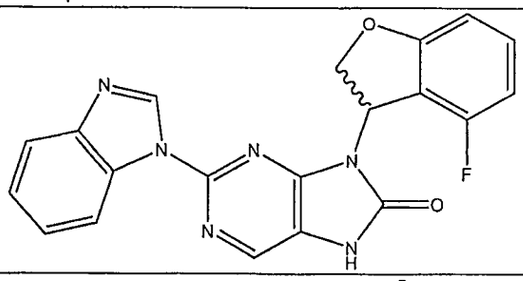
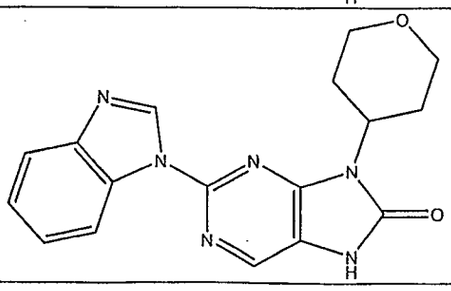
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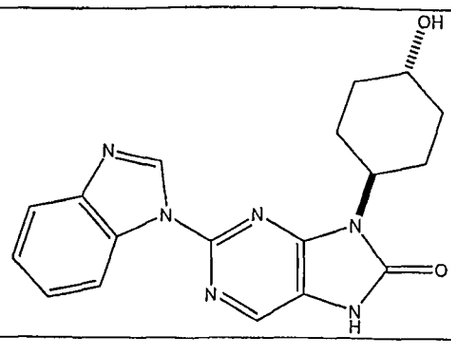
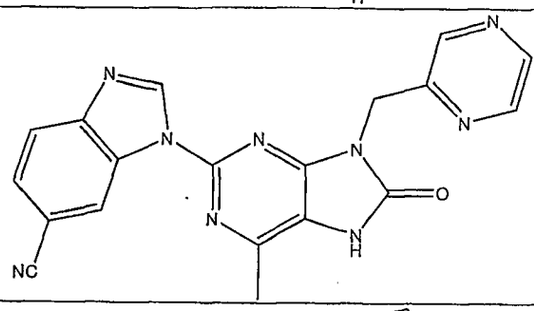
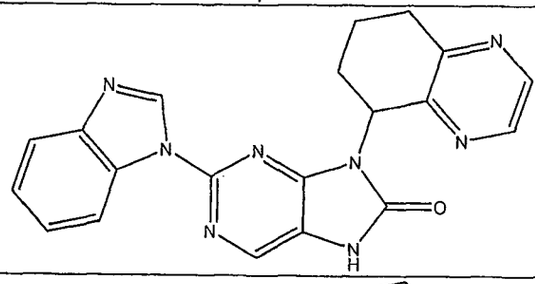
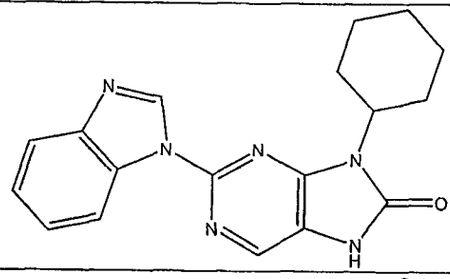
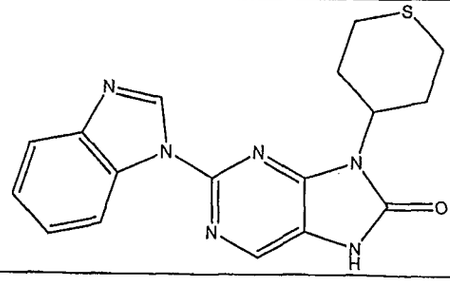
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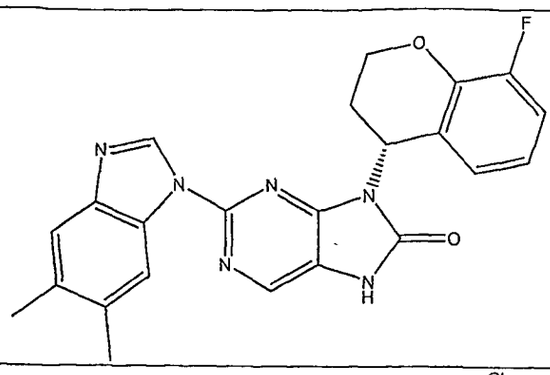
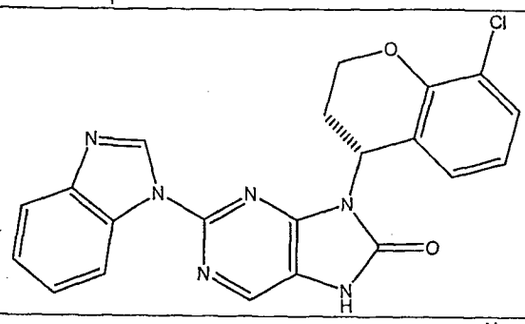
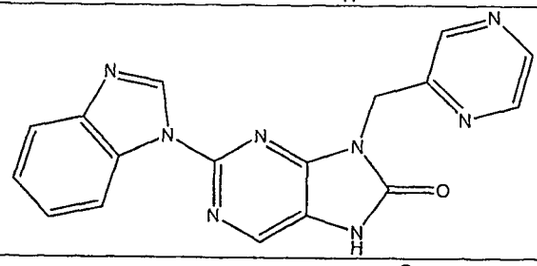
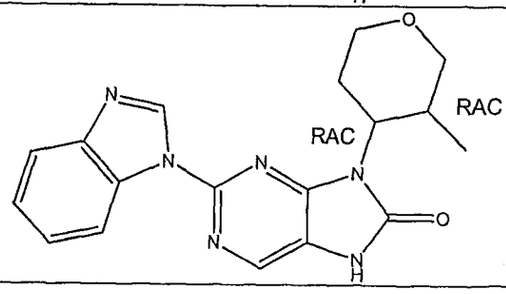
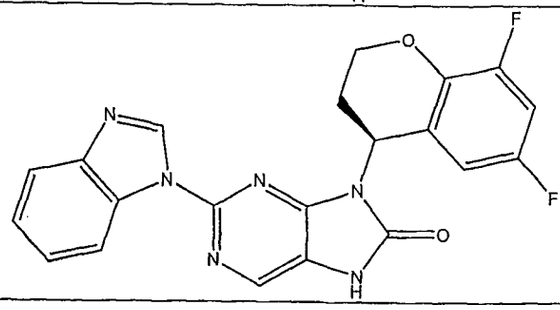
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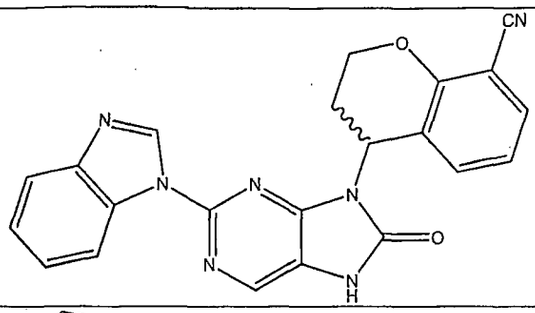
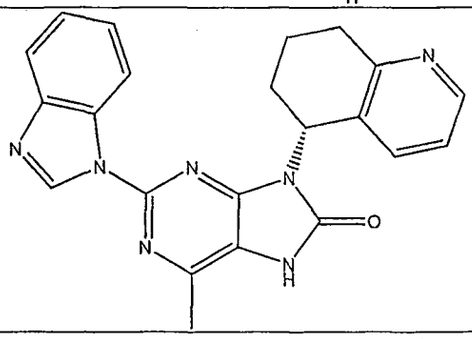
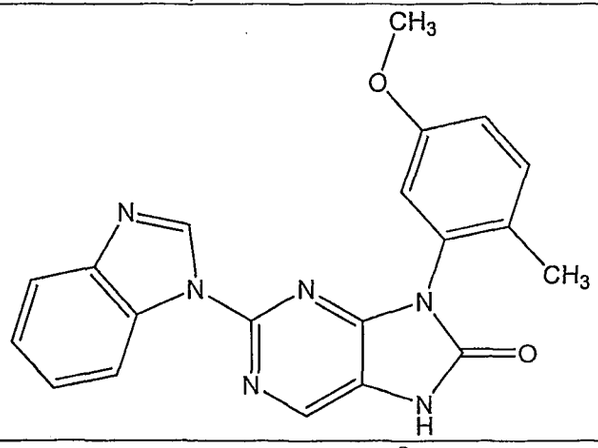
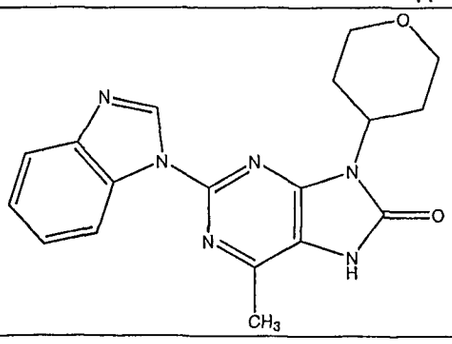
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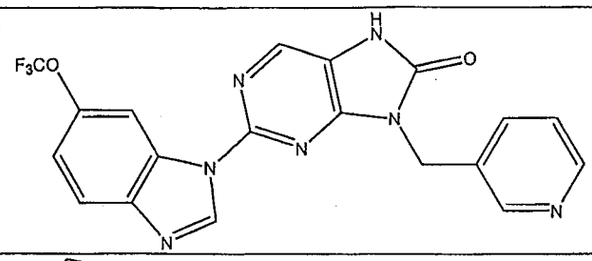
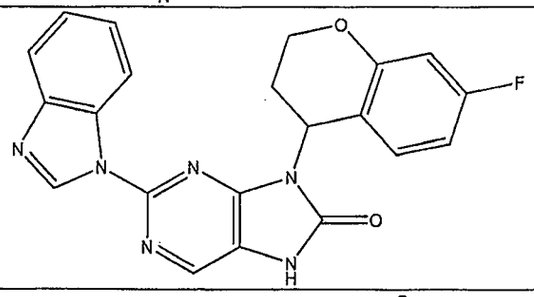
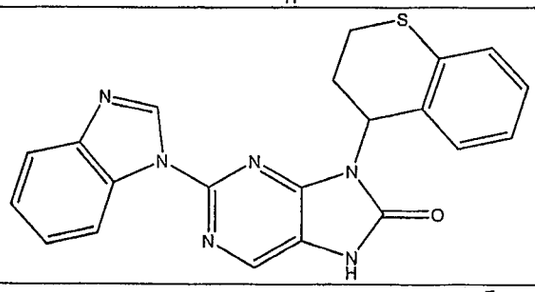
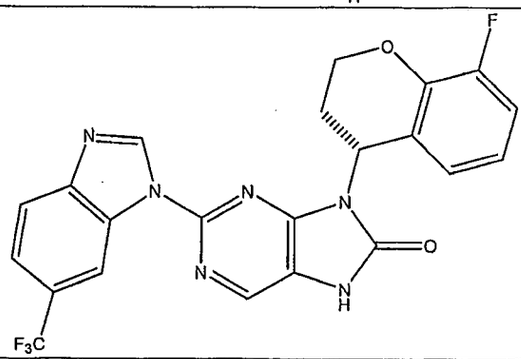
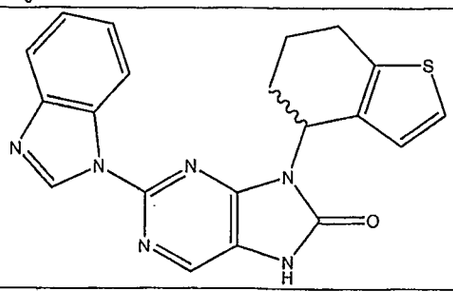
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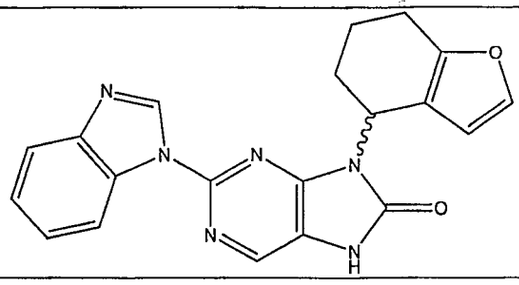
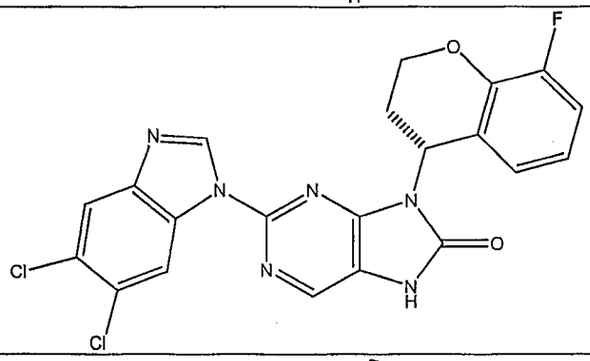
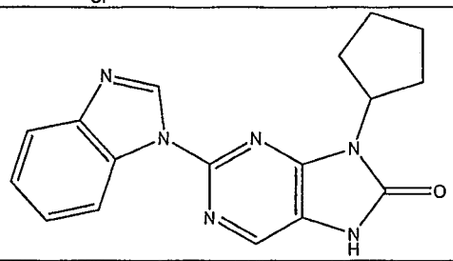
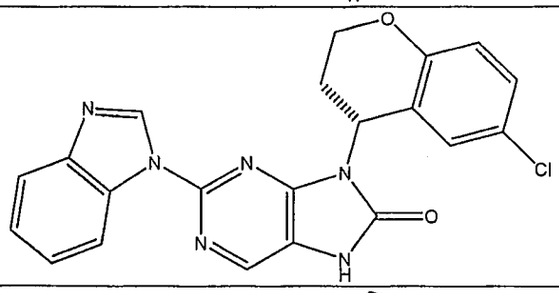
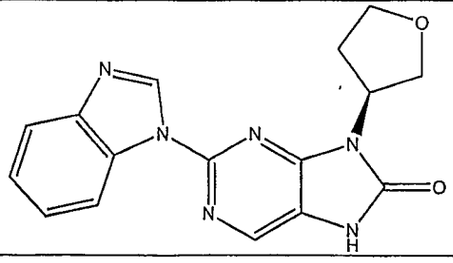
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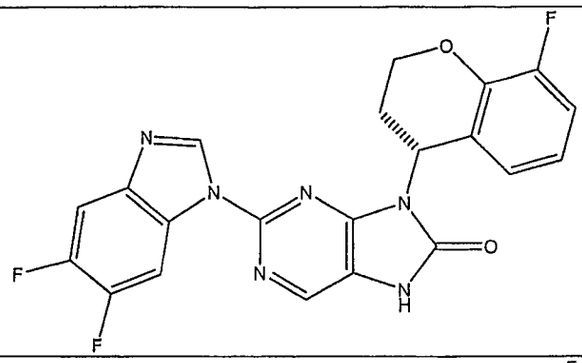
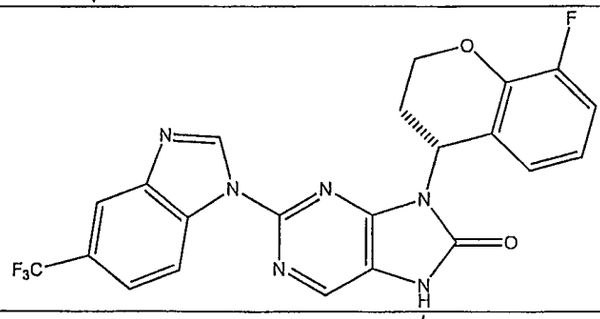
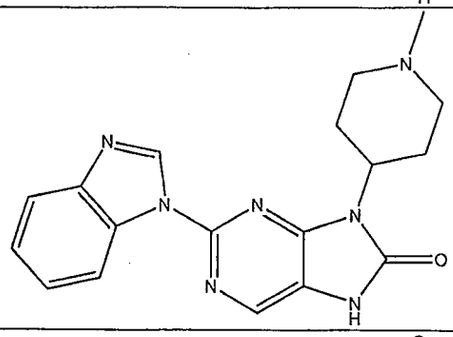
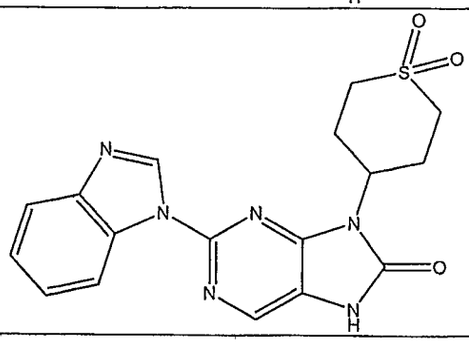
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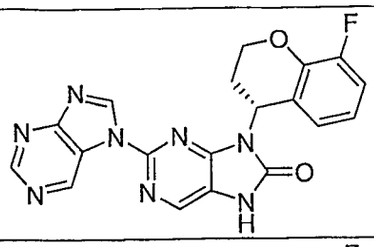
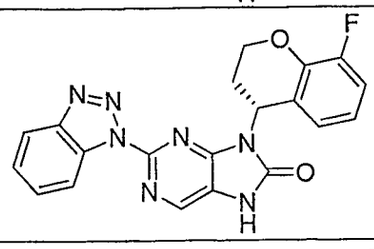
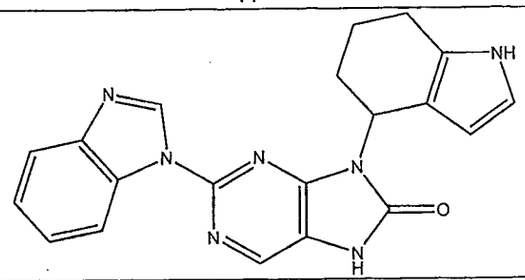
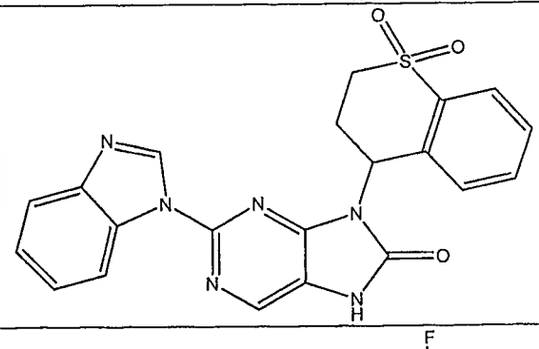
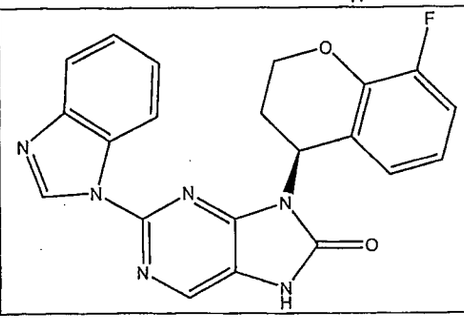
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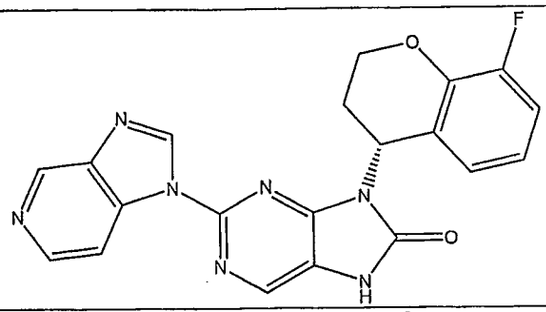
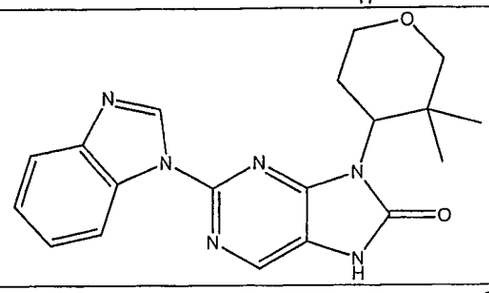
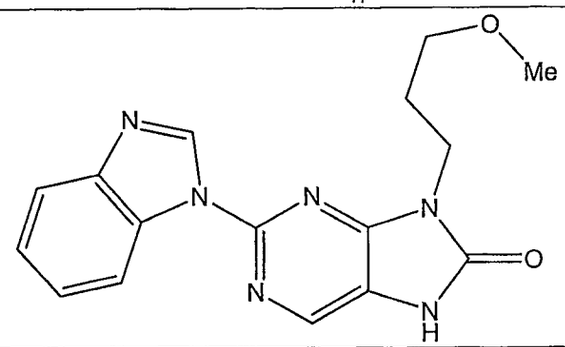
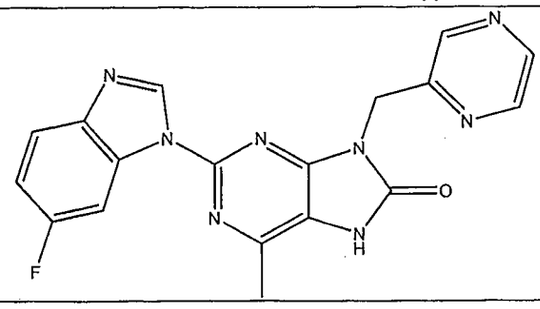
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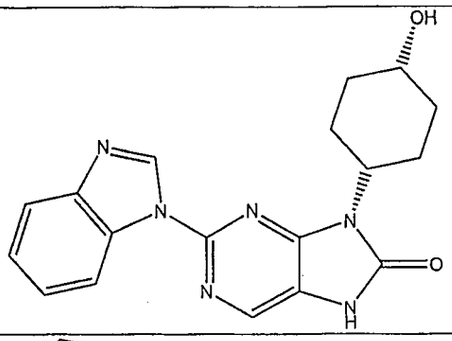
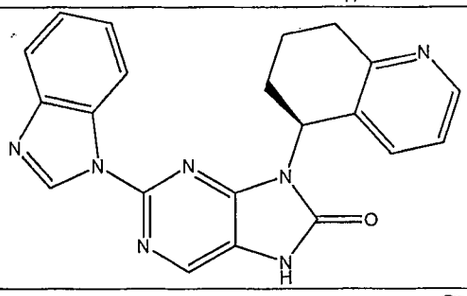
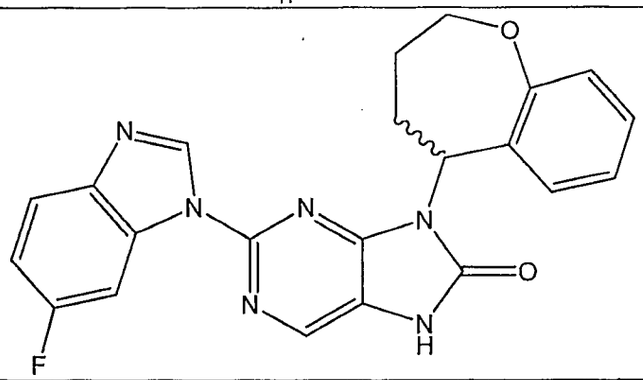
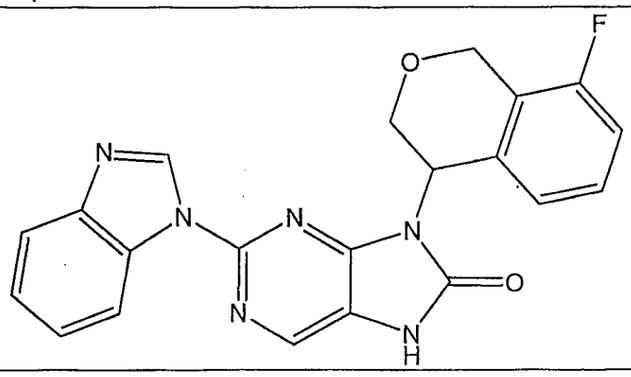
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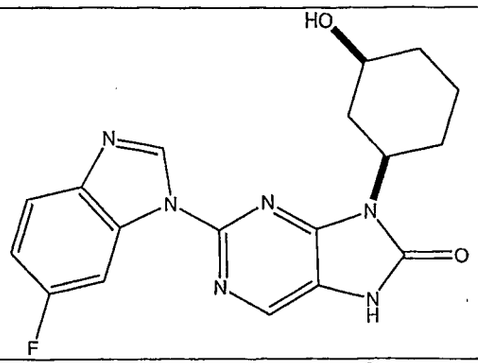
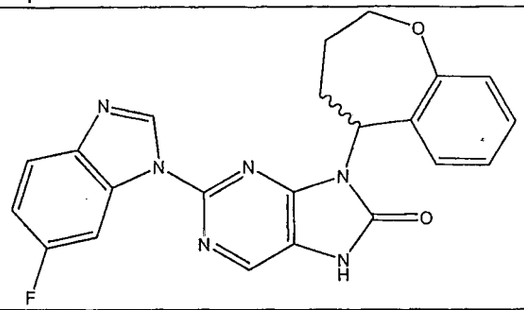
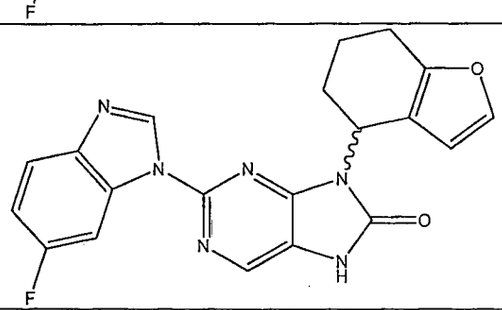
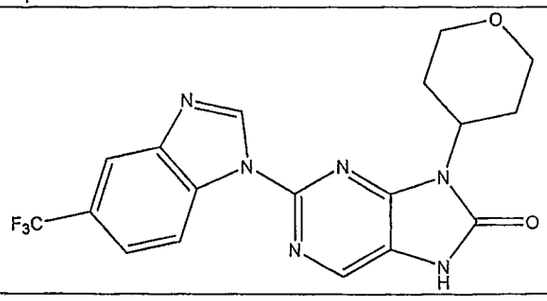
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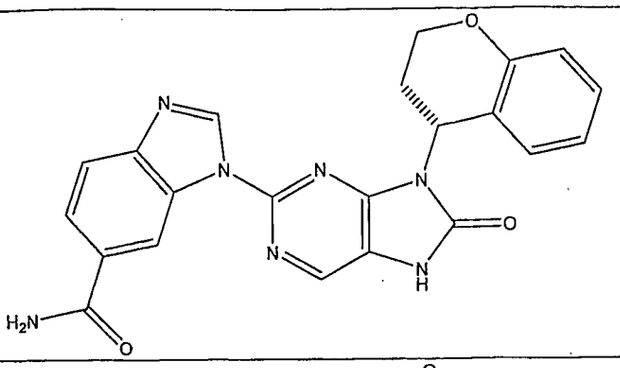
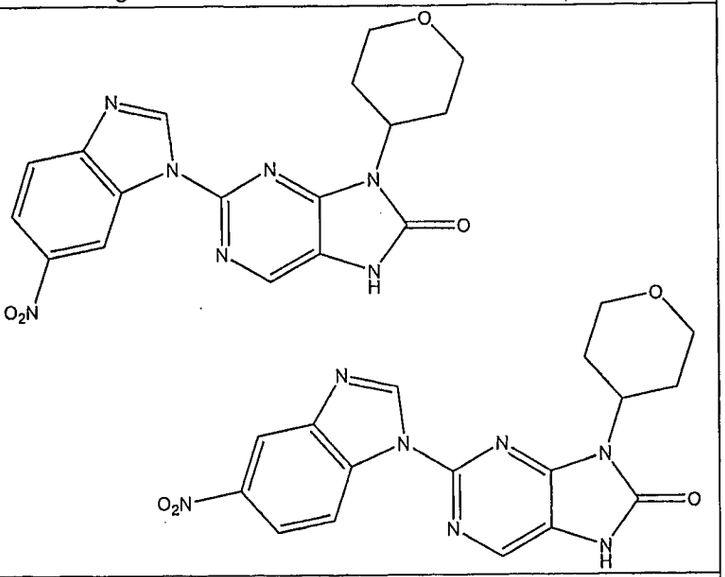
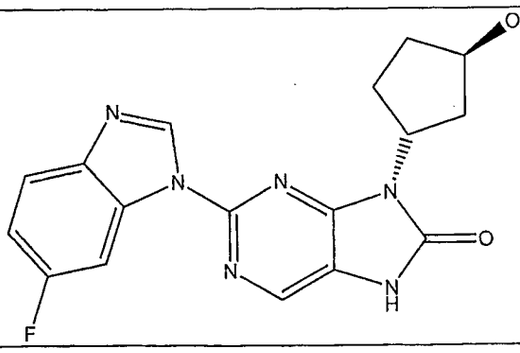
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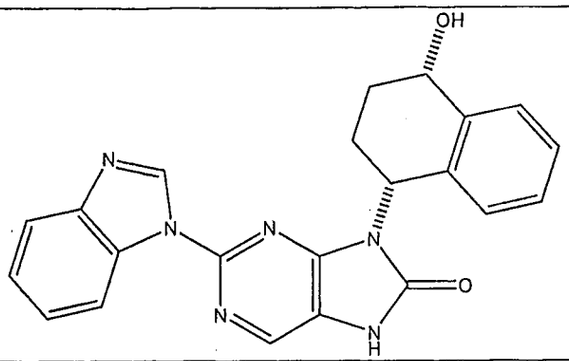
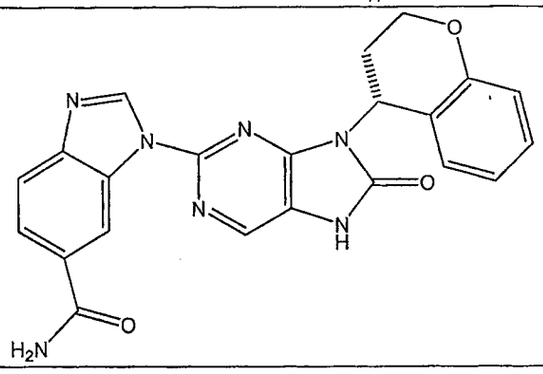
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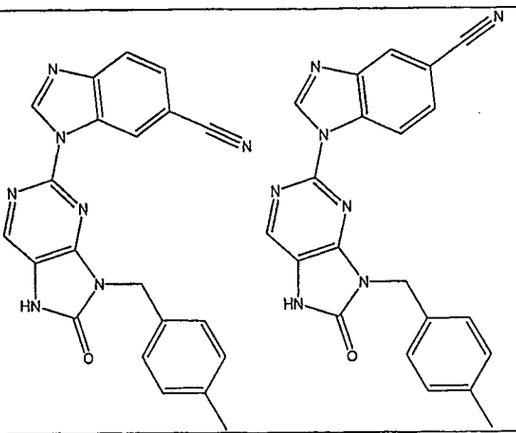
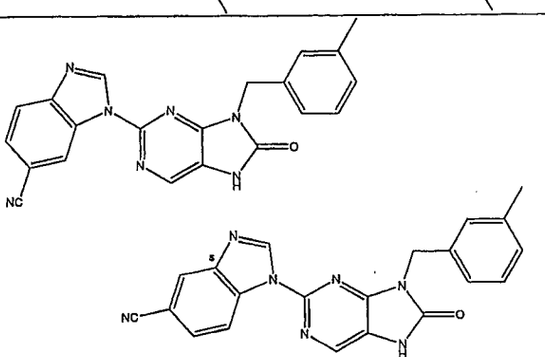
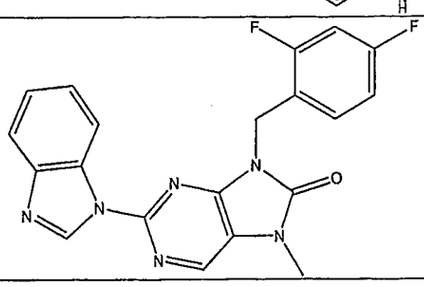
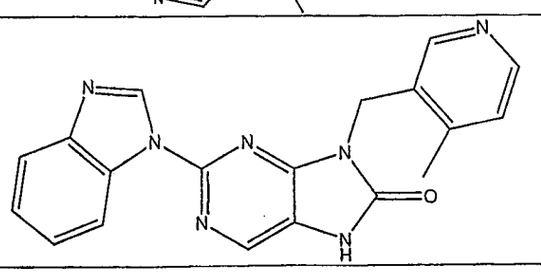
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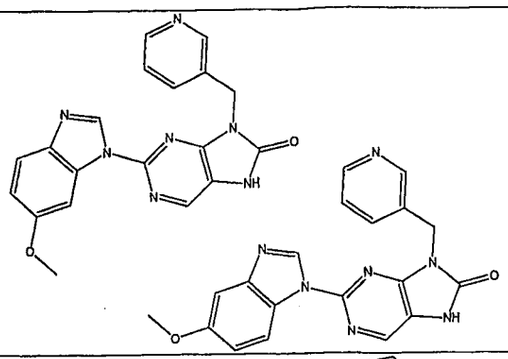
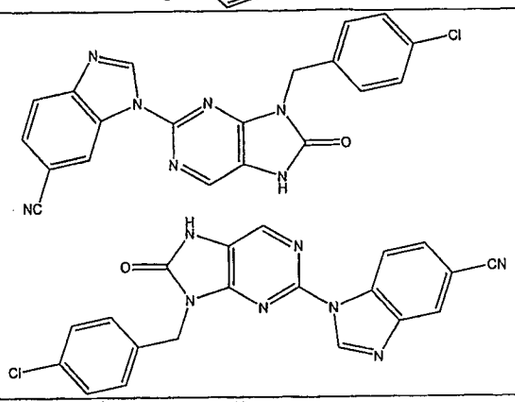
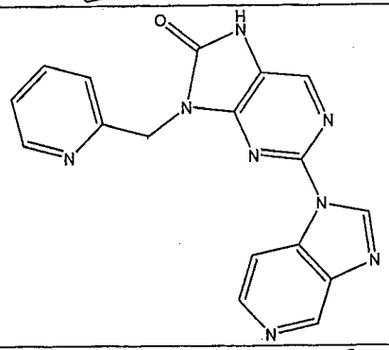
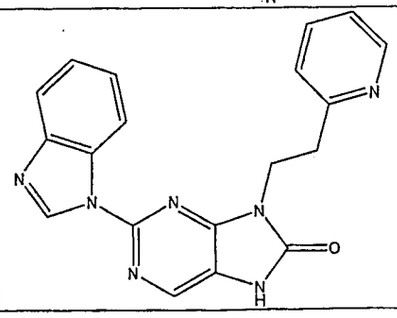
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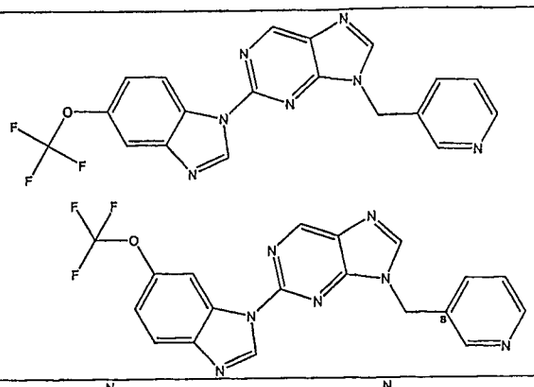
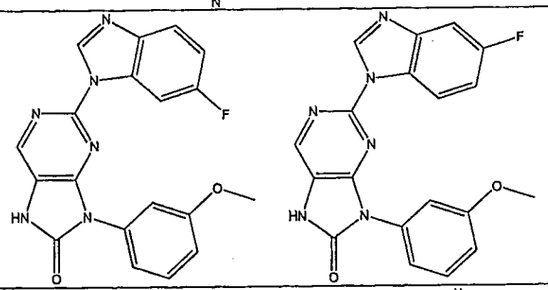
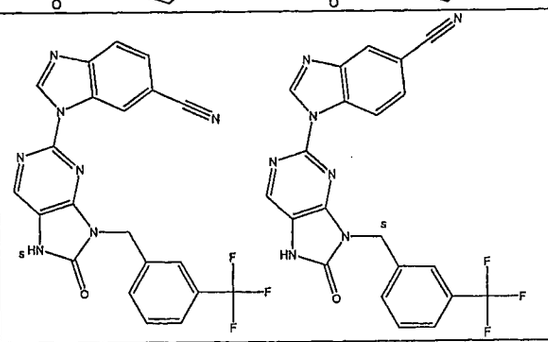
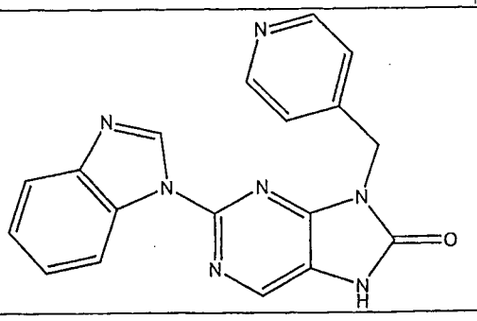
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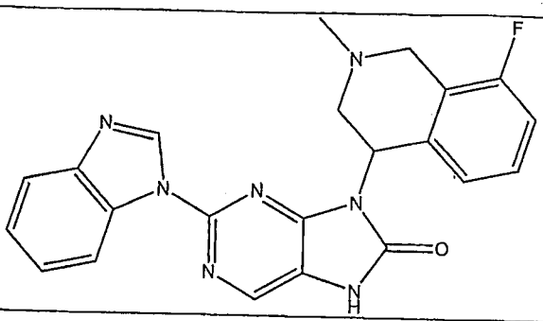
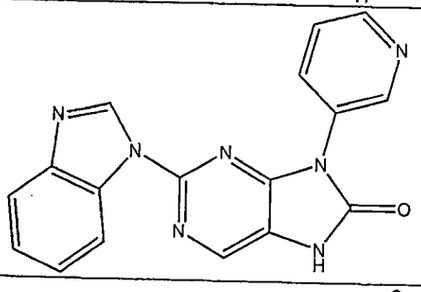
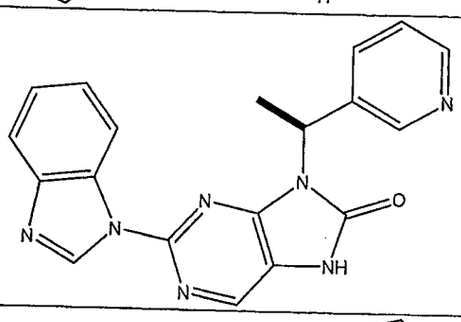
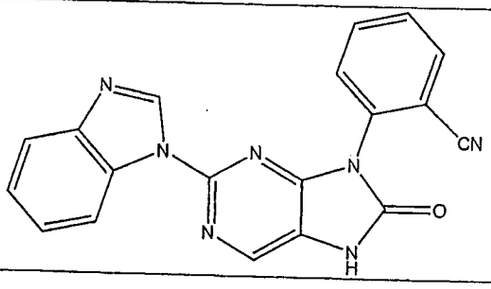
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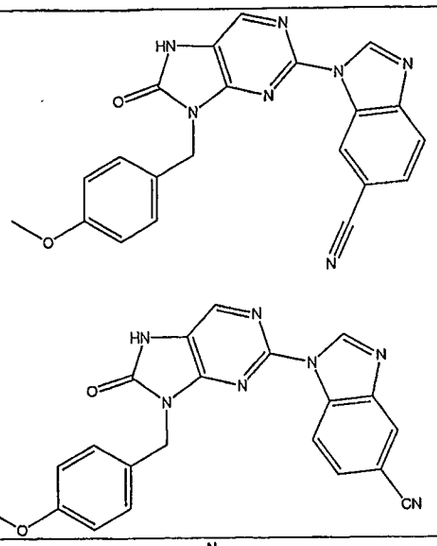
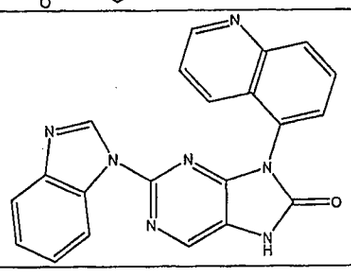
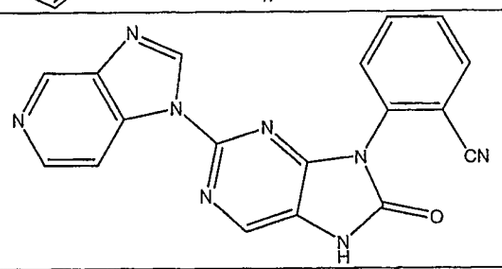
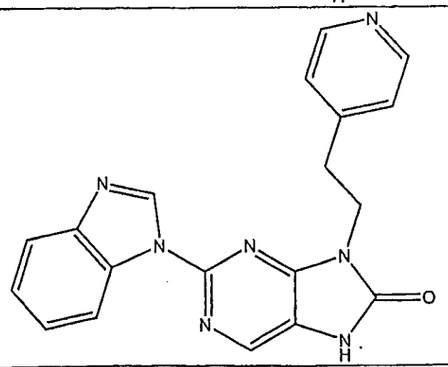
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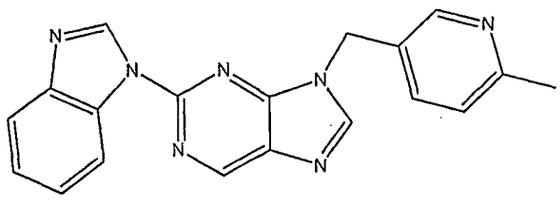
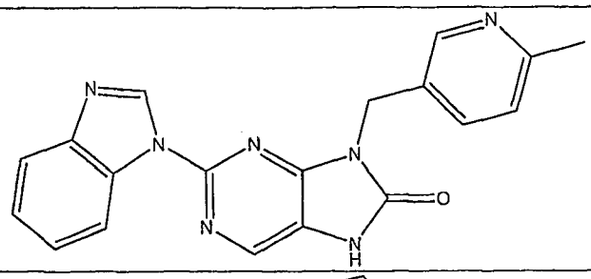
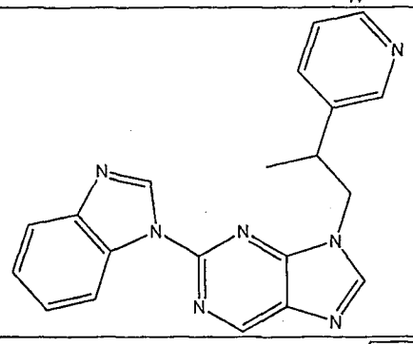
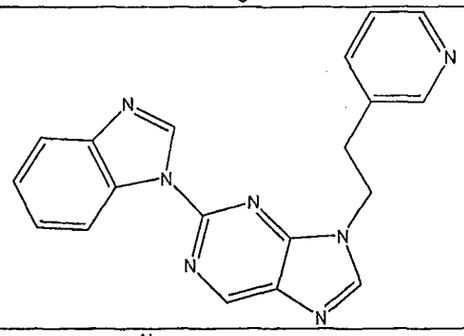
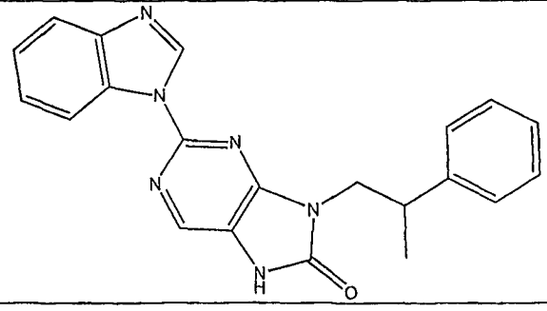
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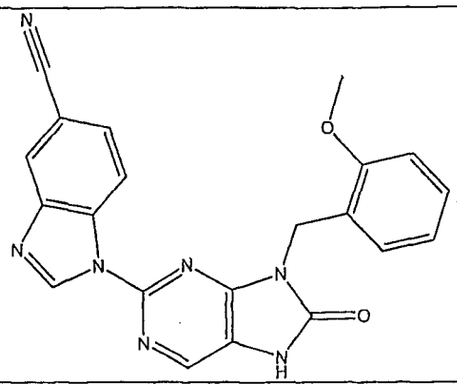
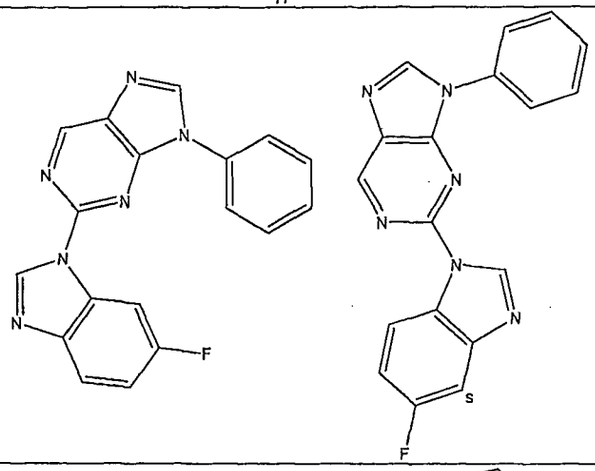
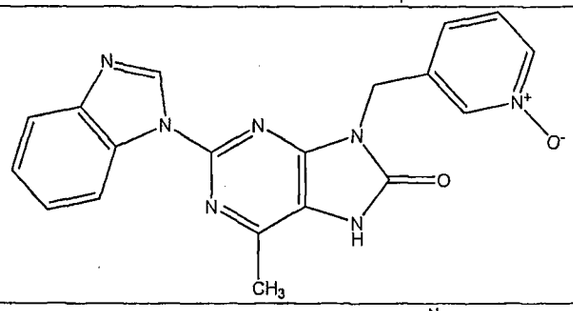
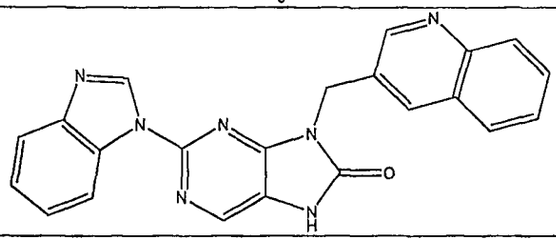
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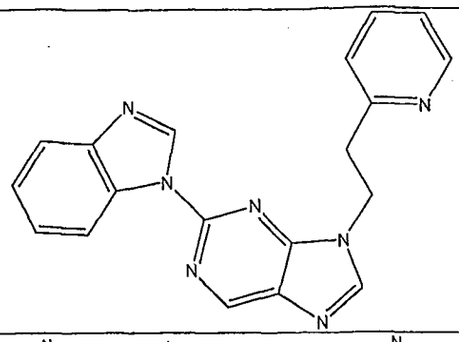
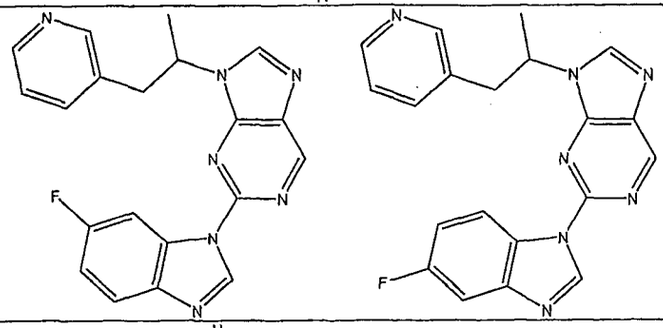
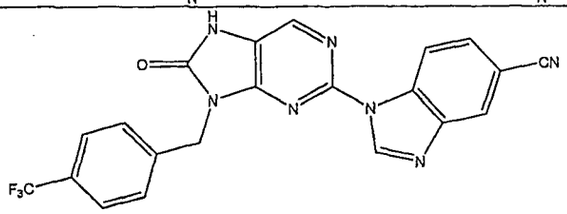
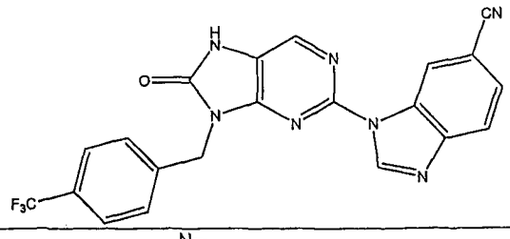
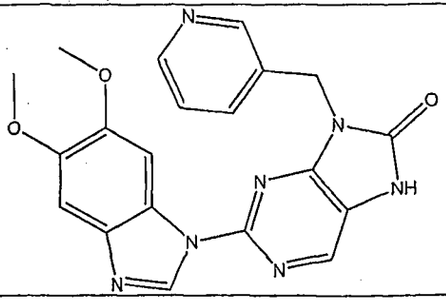
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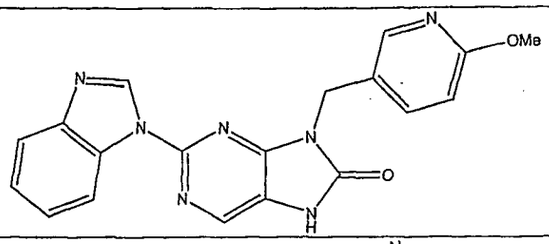
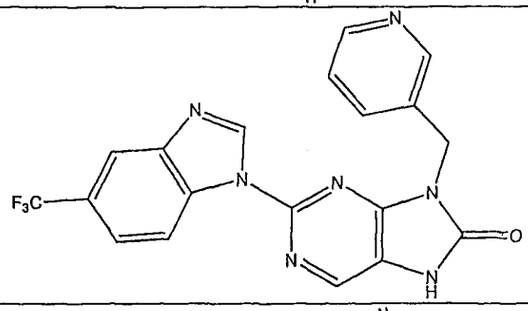
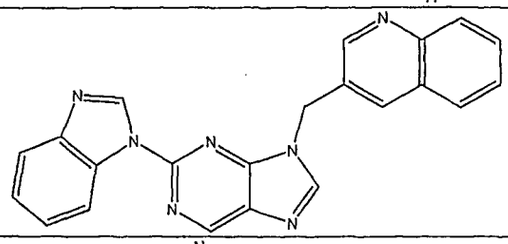
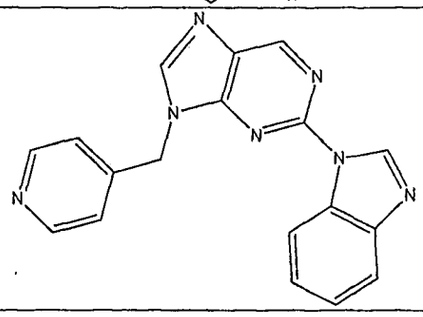
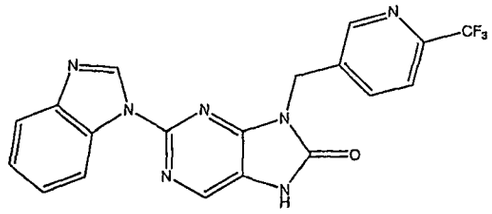
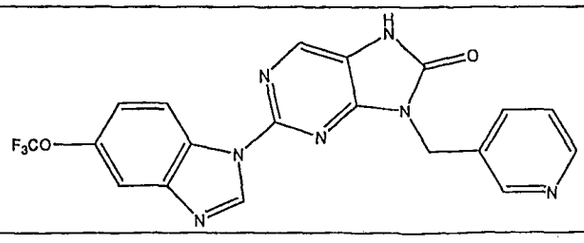
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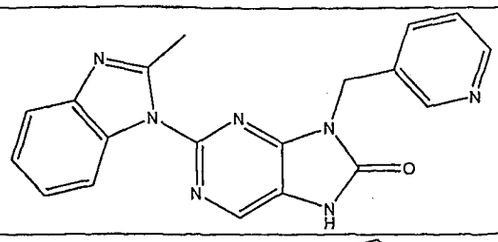
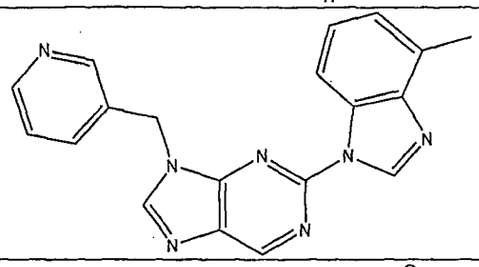
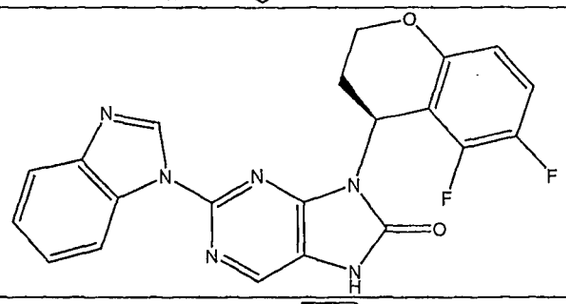
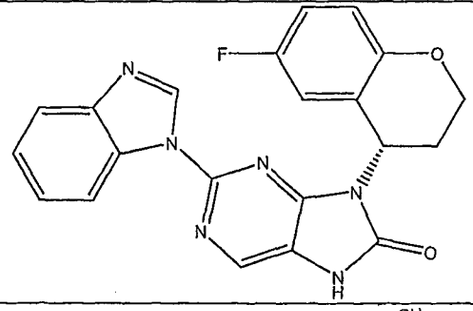
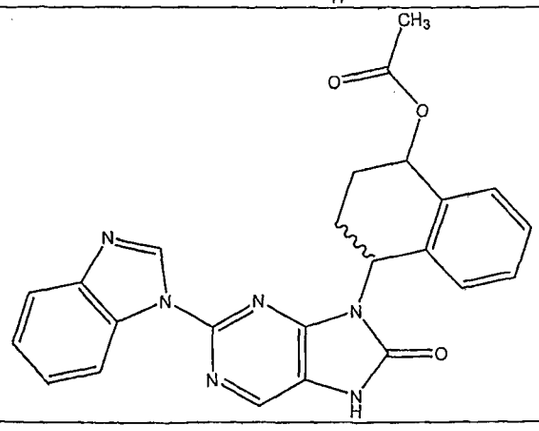
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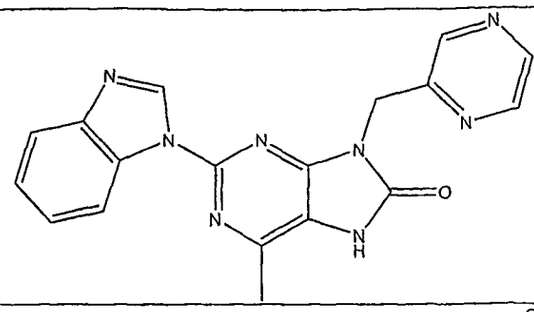
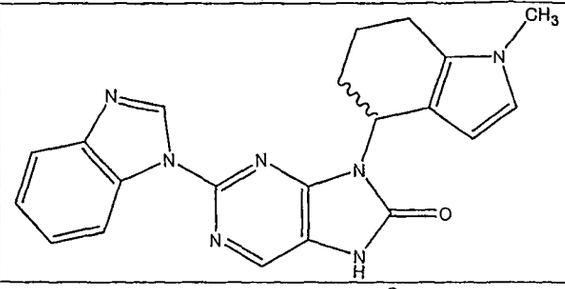
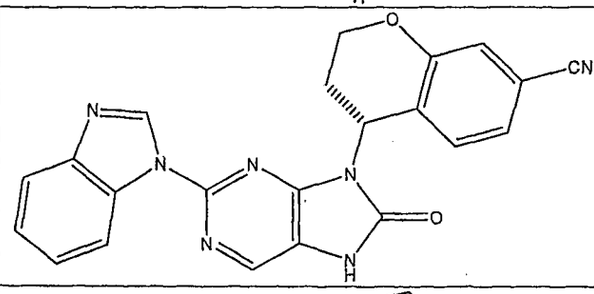
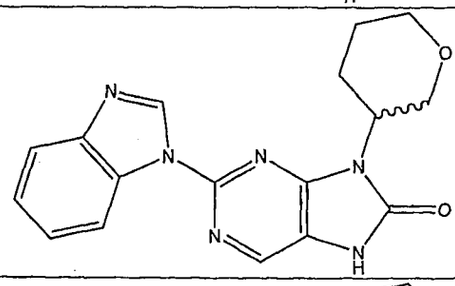
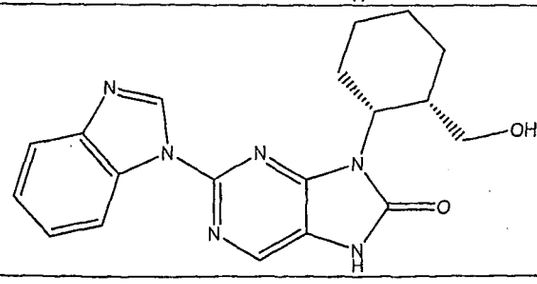
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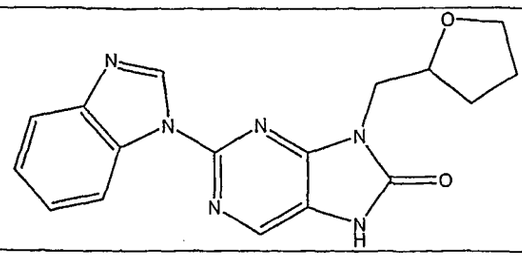
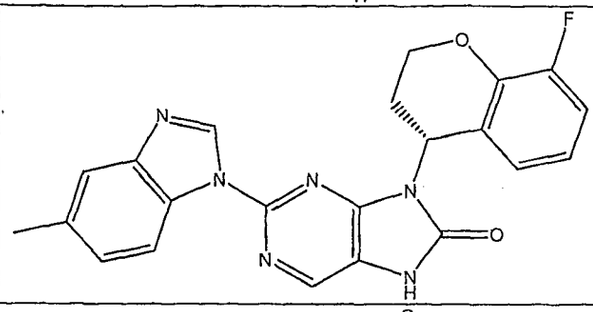
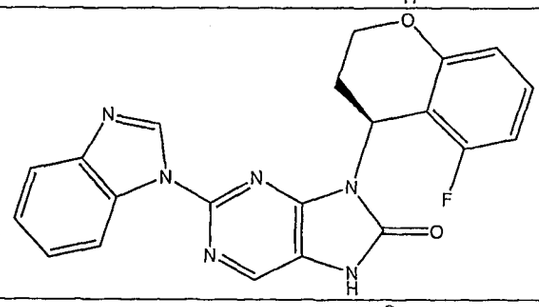
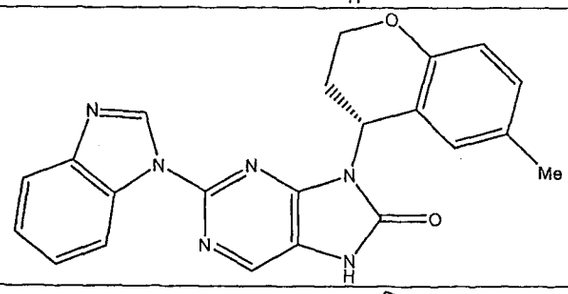
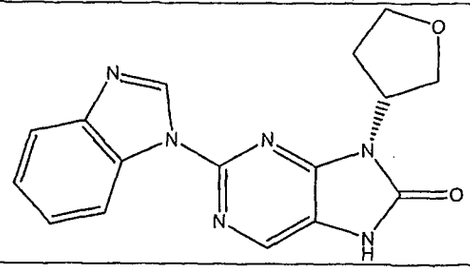
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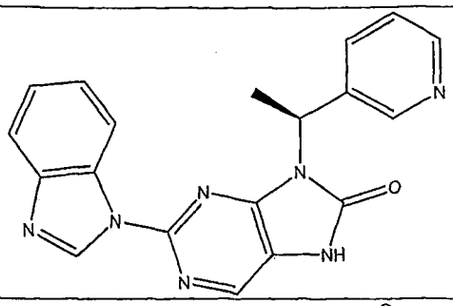
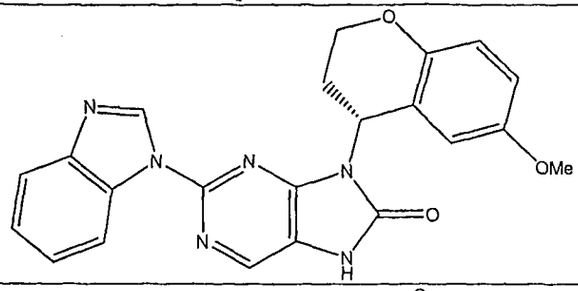
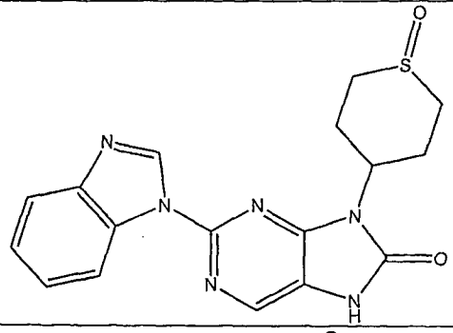
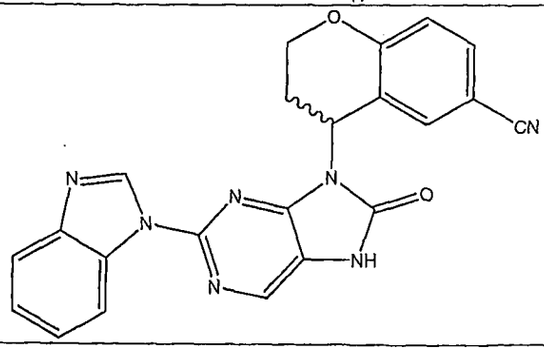
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IL-2-induced IFN-γ production in the mouse

[395] Administration of IL-2 leads to an increase in serum IFN-γ in the mouse due to NK secretion of the cytokine (Thornton S, Kuhn KA, Finkelman FD and Hirsch R. NK cells secrete high levels of IFN-γ in response to in vivo administration of IL-2. Eur J

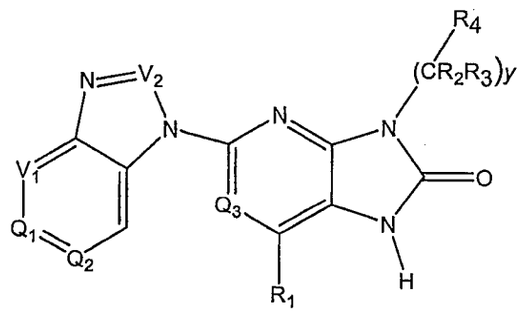
Immunol 2001 31:3355-3360). The experiment was carried out essentially according to the protocol in Thornton et al. and the test compounds were administered in order to determine the level of inhibition attained. In summary, female BALB/c mice were fasted for 12-18 hours before a study but had free access to water at all times. Test compounds were administered by gavage one hour before intraperitoneal injection of IL-2 and capture antibody. At termination of the studies, the mice were sacrificed by carbon dioxide inhalation, terminal blood samples were collected by cardiac puncture and serum was generated. Serum was stored frozen until it was assayed for IFN-γ, as described by the kit manufacturer (BD Pharmingen™, San Diego, CA).

[396] Using the above method, compounds 114, 120, 135, 137, 138, 139, 142, 143, 151, and 162 from Table 1 were shown to inhibit IL-2-induced IFN-gamma production by >40% at 30 mg/kg *in vivo* in the mouse. A reference compound, CP690550, exhibited 96% inhibition at 30 mg/kg in this screen.

[397] Although the foregoing invention has been described in some detail for purposes of illustration, it will be readily apparent to one skilled in the art that changes and modifications may be made without departing from the scope of the invention described herein.

CLAIMS

1. A compound of formula I



I

wherein

Q_1 and Q_2 are independently selected from the group consisting of CX_1, CX_2, and nitrogen;

Q_3 is N or CH;

X_1 and X_2 are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, cyano, halo, halo$(C_1\text{-}C_6)$alkyl, hydroxyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, nitro, carboxamido, and methylsulfonyl;

V_1 and V_2 are independently selected from CH and N;

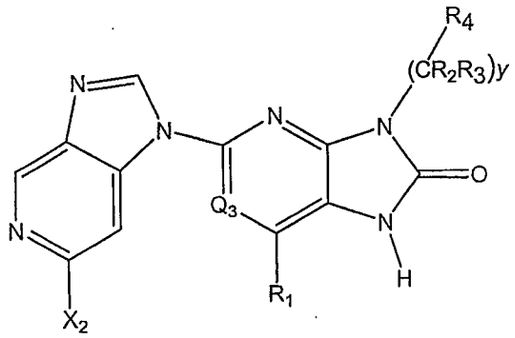
R_1 is selected from the group consisting of hydrogen and methyl;

y is zero or an integer selected from 1, 2 and 3;

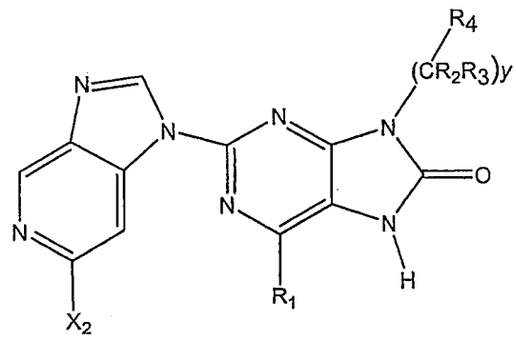
R_2 and R_3 are selected independently for each occurrence of (CR_2R_3) from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl; and

R_4 is selected from a group consisting of alkyl, heterocyclyl, aryl, substituted alkyl, substituted heterocyclyl, and substituted aryl.

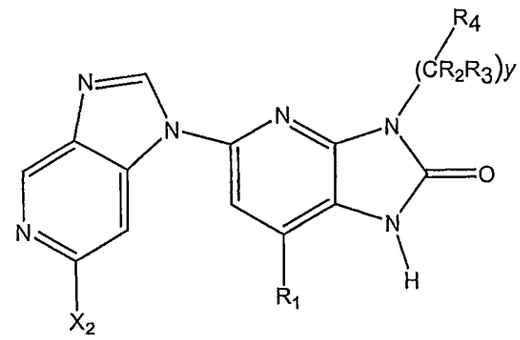
2. A compound according to claim 1 of formula:



3. A compound according to claim 2 of formula:

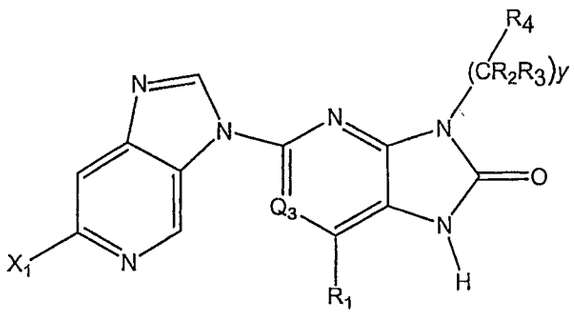


4. A compound according to claim 2 of formula:

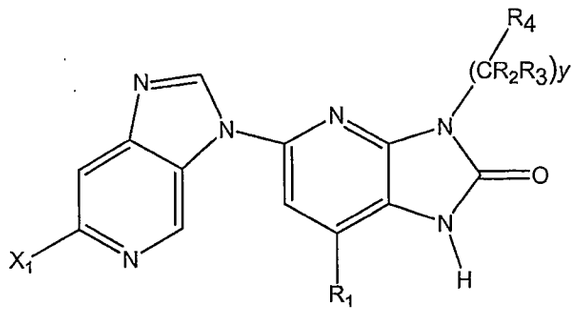


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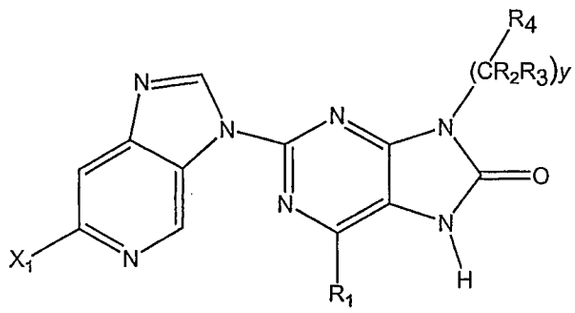
5. A compound according to claim 1 of formula:



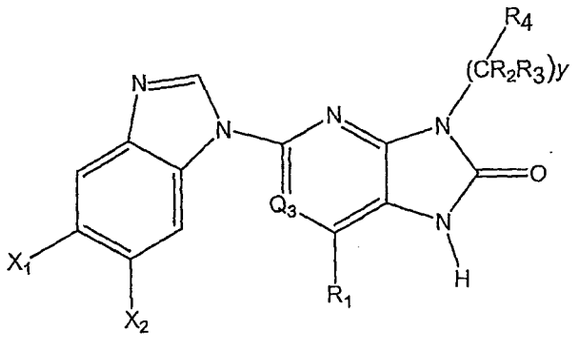
6. A compound according to claim 5 of formula:



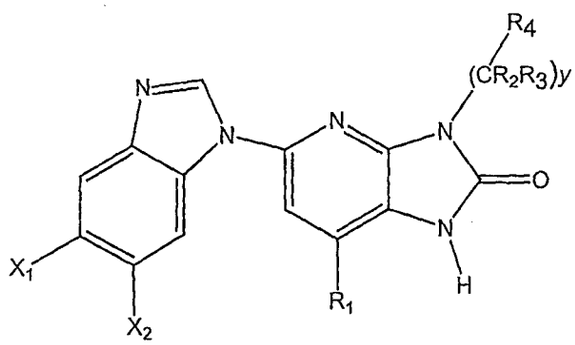
7. A compound according to claim 5 of formula:



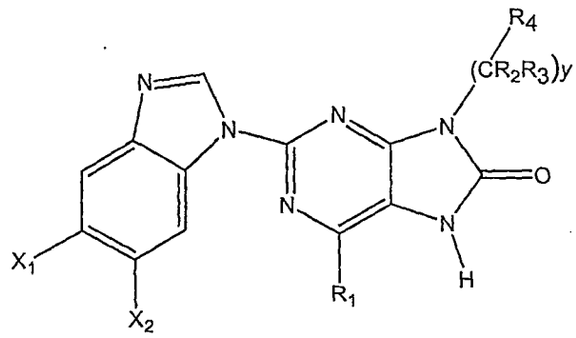
8. A compound according to claim 1 of formula:



9. A compound according to claim 8 of formula:

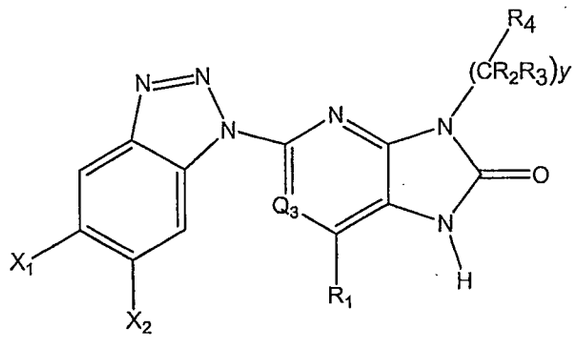


10. A compound according to claim 8 of formula:

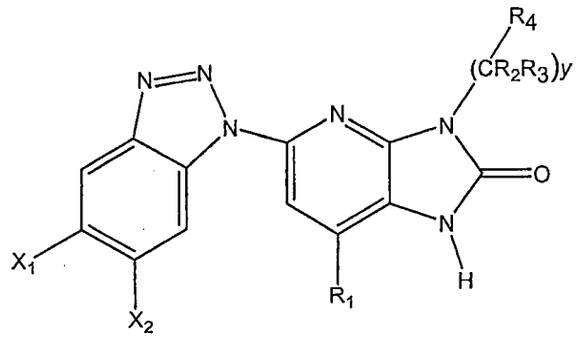


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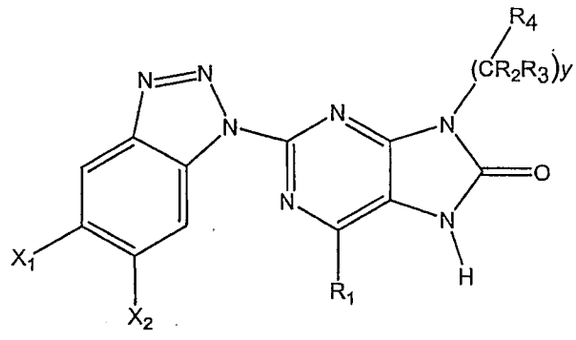
11. A compound according to claim 1 of formula:



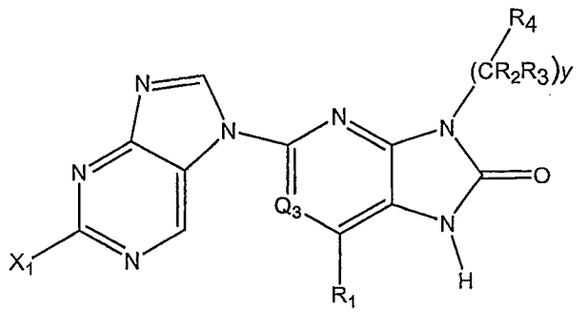
12. A compound according to claim 11 of formula:



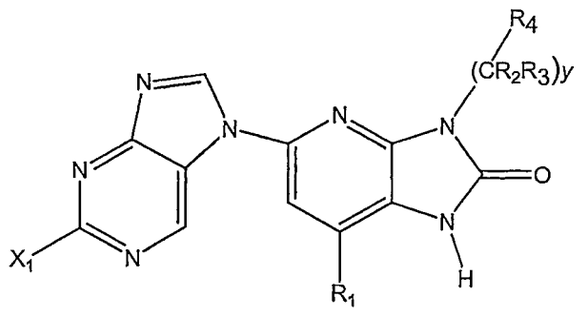
13. A compound according to claim 11 of formula:



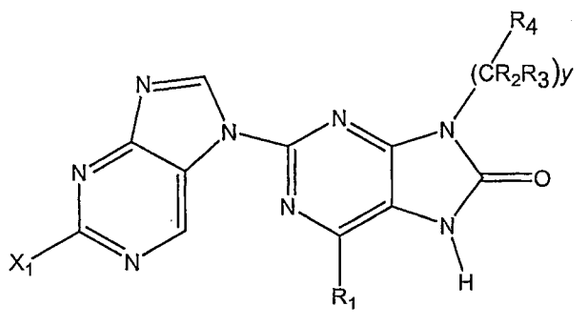
14. A compound according to claim 1 of formula:



15. A compound according to claim 14 of formula:



16. A compound according to claim 14 of formula:



17. A compound according to any of claims 1-16 wherein X_1 and X_2 are independently selected from hydrogen, cyano, chloro, fluoro, methyl, trifluoromethyl and trifluoromethoxy, carboxamido.

18. A compound according to any of claims 8-13 wherein X_1 is hydrogen and X_2 is chosen from hydrogen, cyano, chloro, fluoro, methyl, carboxamido, and trifluoromethyl.

19. A compound according to any of claims 1-16 wherein R_1 is H.

20. A compound according to any of claims 1-16 wherein, y is 1 or 2 and R_2 and R_3 are hydrogen or methyl.

21. A compound according to claim 20, wherein R_4 is selected from phenyl, quinoline, pyridine, pyrazine and their substituted counterparts.

22. A compound according to any of claims 1-16 wherein y is zero.

23. A compound according to claim 22, wherein R_4 is selected from a monocycle, bicycle, or substituted monocycle or substituted bicycle containing at least one oxygen atom or nitrogen atom.

24. A compound according to claim 22, wherein R_4 is chosen from cyclopentyl, cyclohexyl, phenyl, tetralin, piperidine, oxepane, benzoxepane, tetrahydropyran, tetrahydrofuran, tetrahydroindole, tetrahydroisoquinoline, quinoline, tetrahydroquinoline, chroman, pyridine, dihydrocyclopenta[b]pyridine, dihydrobenzofuran, tetrahydrobenzofuran, tetrahydrobenzothiophene, dihydrobenzothiophene, dihydropyrano[2,3-b]pyridine, tetrahydroquinoxaline, tetrahydrothiopyran (thiane), thiochroman (dihydrobenzothiin), thiochroman-1,1-dioxide, tetrahydronaphthalene, oxa-bicyclooctane, oxocane, tetrathiohydropryan-1,1-dioxide, tetrathiohydropryanoxide, and their substituted counterparts.

25. A compound according to claim 22, wherein R_4 is cycloalkyl substituted with OH, alkoxy, hydroxyalkyl, oxo, carboxamido, carboxy, or alkoxycarbonyl.

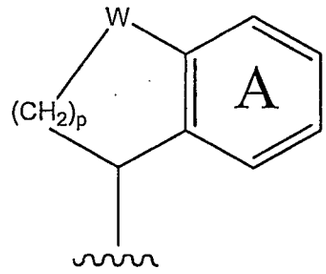
26. A compound according to claim 22 wherein R_4 is selected from cyclopentyl, cyclohexyl, phenyl, indane, tetralin, piperidine, oxepane, benzoxepane, dihydrocyclopentapyridine, tetrahydropyran, tetrahydrofuran, tetrahydroindole, isoquinoline, tetrahydroisoquinoline, quinoline, tetrahydroquinoline, chroman, isochroman, pyridine, dihydrocyclopental[b]pyridine, pyrimidine, dihydropyran, dihydrobenzofuran, tetrahydrobenzofuran, tetrahydrobenzothiophene, dihydrobenzothiophene, furan, dihydropyrano[2,3-b]pyridine, tetrahydroquinoxaline, tetrahydrothiopyran (thiane), thiochroman (dihydrobenzothiin), thiochroman-1,1-dioxide, tetrahydronaphthalene, oxa-bicyclooctane, oxocane, tetrahydrothiopyran-1,1-dioxide, tetrahydrothiopyran oxide, and their substituted counterparts.

27. A compound according to any of claims 1-16 wherein,
(a) y is zero and R_4 is selected from cyclohexyl, tetralin, indane, oxepane, benzoxepane, dihydrocyclopentapyridine, tetrahydropyran, tetrahydroquinoline, chroman, dihydrobenzofuran, tetrahydrobenzofuran, dihydropyrano[2,3-b]pyridine and tetrahydroquinoxaline, each optionally substituted with hydroxy, oxo, or halogen; or
(b) y is 1 or 2, R_2 and R_3 are hydrogen or methyl and R_4 is selected from phenyl, pyridine and pyrazine, each optionally substituted with halogen.

28. A compound according to claim 27 wherein y is 0 and R_4 is chosen from chroman-4-yl; 3,4-dihydronaphthalen-1(2*H*)-on-4-yl; 2,3-dihydroinden-1-on-4-yl and their fluoro substituted counterparts.

29. A compound according to claim 28 wherein R_4 is chroman-4-yl and the carbon at 4 of the chroman is of the (R) configuration.

30. A compound according to claim 27 wherein y is 0 and R_4 is



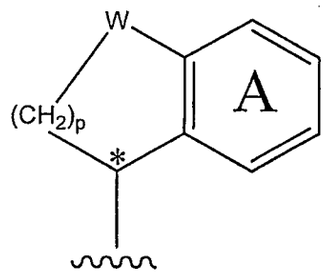
wherein

W is CH_2, C=O, O, and CHOH;

p is 1, 2 or 3;

A is a six-membered heteroaromatic ring containing 1 or 2 nitrogens, a benzene ring optionally substituted with one or two fluorines, or a five-membered heterocyclic ring; and the wavy line is the point of attachment to the purinone.

31. A compound according to claim 30 wherein the carbon marked with an asterisk



is of the (R) configuration.

32. A compound according to claim 1, wherein Y is 0 and R_4 is a monocyclic carbocycle or bridged bicyclic carbocycle optionally substituted with one or more OH, alkoxy, hydroxyalkyl, oxo, carboxamido, carboxy, and alkoxycarbonyl.

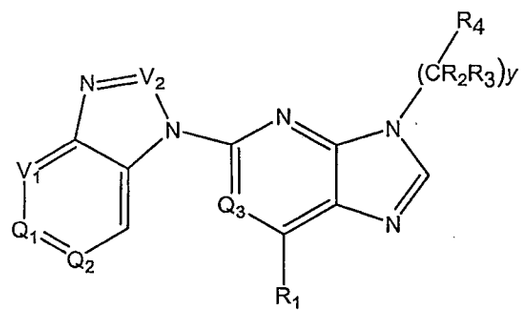
33. A compound according to claim 1, wherein Y is 0 and R_4 is a heterocycle containing at least one nitrogen atom and optionally substituted with OH, alkoxy, hydroxyalkyl, oxo, acyl, carboxamido, carboxy, and alkoxycarbonyl.

34. A compound according to claim 33, wherein R_4 is a monocyclic heterocycle.

35. A compound according to claim 27 wherein y is 1 and R_4 is selected from difluorophenyl, fluorophenyl, chlorophenyl, chlorofluorophenyl, pyridin-3-yl and pyrazin-3-yl.

36. A compound according to claim 27 wherein y is zero and R_4 is selected from tetrahydropyran-4-yl, 4-hydroxycyclohexyl, 4-loweralkoxycyclohexyl, 4-oxocyclohexyl and oxepan-4-yl.

37. A compound of formula II



II

wherein

Q_1 and Q_2 are independently selected from the group consisting of CX_1, CX_2, and nitrogen;

Q_3 is N or CH;

X_1 and X_2 are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, cyano, halo, halo$(C_1\text{-}C_6)$alkyl, hydroxyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, nitro, carboxamido, and methylsulfonyl;

V_1 and V_2 are independently selected from CH and N;

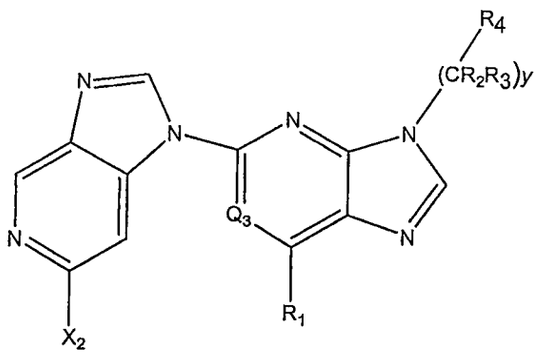
R_1 is selected from the group consisting of hydrogen and methyl;

y is zero or an integer selected from 1, 2 and 3;

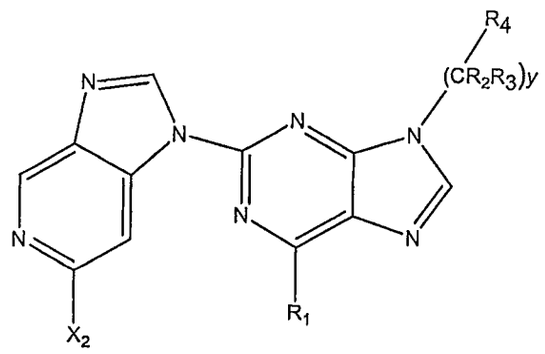
R_2 and R_3 are selected independently for each occurrence of (CR_2R_3) from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl; and

R_4 is selected from a group consisting of alkyl, heterocyclyl, aryl, substituted alkyl, substituted heterocyclyl, and substituted aryl.

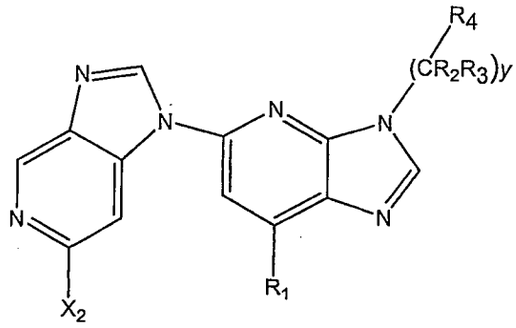
38. A compound according to claim 37 of formula:



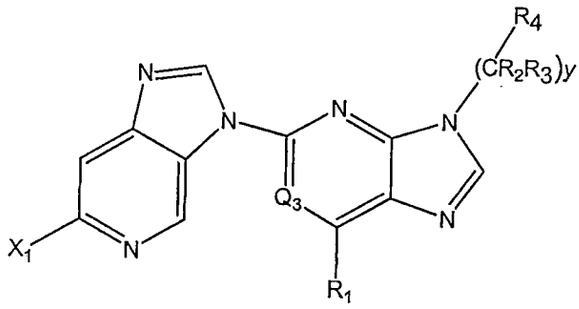
39. A compound according to claim 38 of formula:



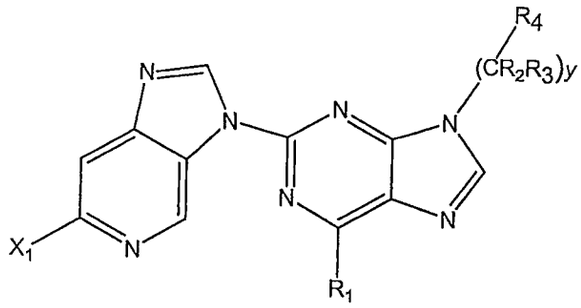
40. A compound according to claim 38 of formula:



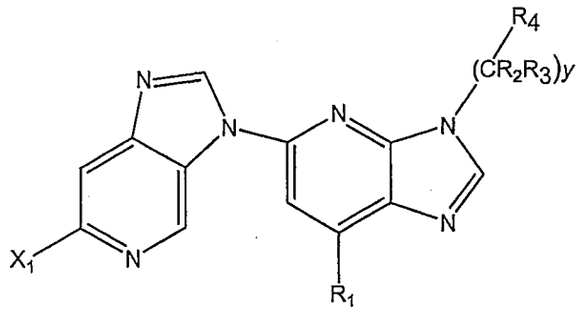
41. A compound according to claim 37 of formula:



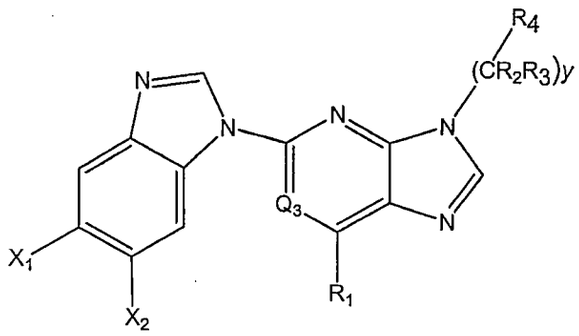
42. A compound according to claim 41 of formula:



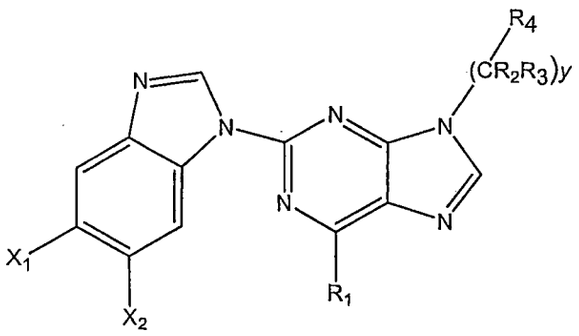
43. A compound according to claim 41 of formula:



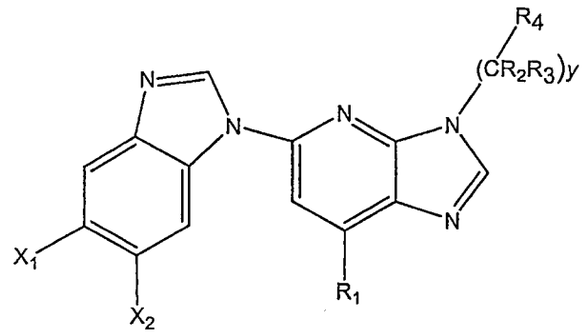
44. A compound according to claim 37 of formula:



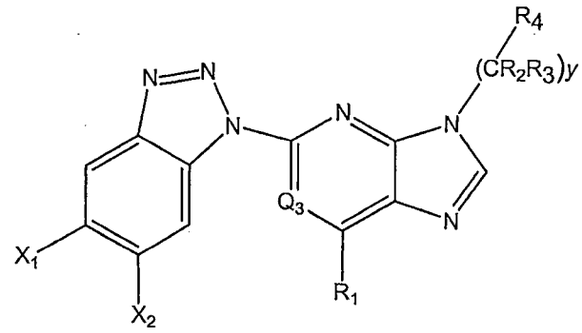
45. A compound according to claim 44 of formula:



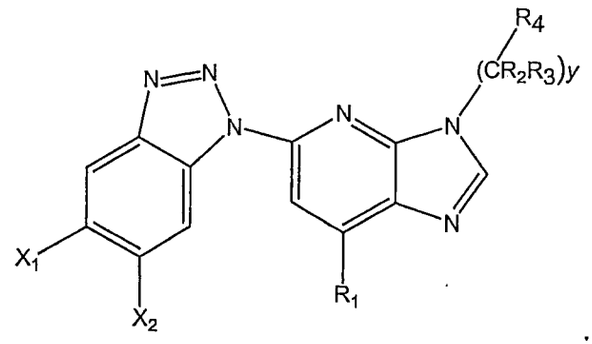
46. A compound according to claim 44 of formula:



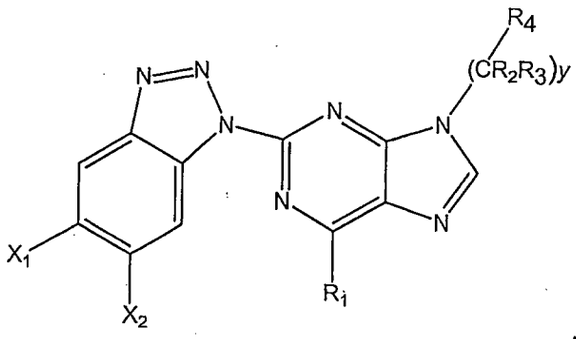
47. A compound according to claim 37 of formula:



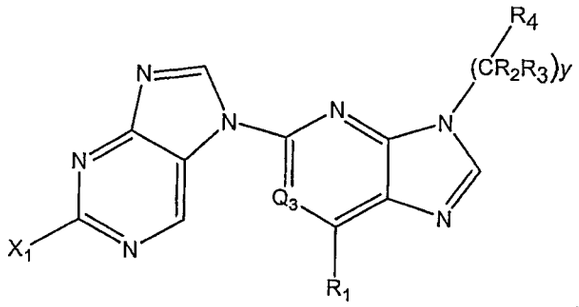
48. A compound according to claim 47 of formula:



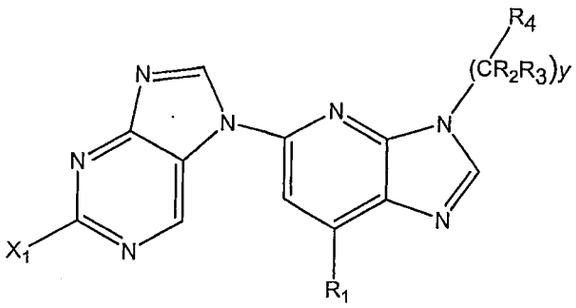
49. A compound according to claim 47 of formula:



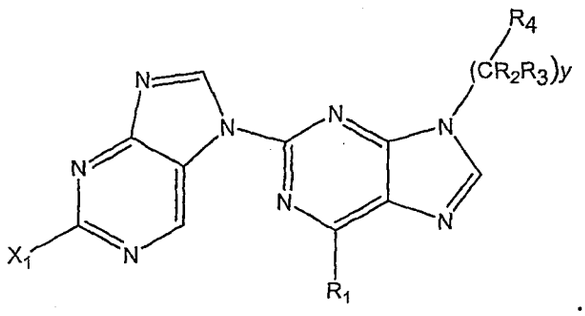
50. A compound according to claim 37 of formula:



51. A compound according to claim 50 of formula:



52. A compound according to claim 50 of formula:



53. A compound according to any of claims 37-52 wherein X_1 and X_2 are independently selected from hydrogen, cyano, fluoro, methyl, trifluoromethyl, carboxamido, and trifluoromethoxy.

54. A compound according to any of claims 37-52 wherein R_1 is H.

55. A compound according to any of claims 37-52 wherein y is 1 or 2 and R_2 and R_3 are hydrogen or methyl.

56. A compound according to claim 55 wherein R_4 is selected from phenyl, pyridine, pyrazine, quinoline and their substituted counterparts.

57. A compound according to any of claims 37-52 wherein y is zero.

58. A compound according to claim 57 wherein R_4 is selected from a monocycle, bicycle, or substituted monocycle or substituted bicycle containing at least one oxygen atom or nitrogen atom.

59. A compound according to claim 57 wherein R_4 is chosen from chroman, tetrahydropyran, quinoline, tetrahydroquinoline, and phenyl.

60. A compound according to claim 57 wherein R_4 is selected from phenyl, tetralin, indane, isoquinoline, tetrahydroquinoline, tetrahydropyran and their substituted counterparts.

61. A compound according to claim 55 wherein y is 1 and R_4 is selected from difluorophenyl, fluorophenyl, chlorophenyl, chlorofluorophenyl, pyridin-3-yl and pyrazin-3-yl.

62. A compound according to claim 55 wherein y is zero and R_4 is chosen from chroman-4-yl; 3,4-dihydronaphthalen-1(2*H*)-on-4-yl; 2,3-dihydroinden-1-on-4-yl and their fluoro substituted counterparts.

63. A compound according to claim 55 wherein y is zero and R_4 is isoquinolin-8-yl or 1,2,3,4-tetrahydroquinolin-5-yl.

64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound according to any of claims 1-16 or 37-52.

65. A method of treating a disorder which is dependent upon inhibition of Janus kinase 3, which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound according to claim 1.

66. A method of treating a disorder which is dependent upon inhibition of Janus kinase 3, which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound according to claim 37.

67. The method according to either of claims 65 or 66 wherein said disorder is selected from an autoimmune disease, an inflammatory disease, a mast cell mediated disease,

cancer, hematological malignancy, organ transplant rejection, and cardiovascular disease.

68. The method according to claim 67 wherein said disorder is organ transplant rejection.

69. The method according to claim 67 wherein said organ transplant is a kidney transplant.

70. The method according to claim 65 or 66 wherein said disorder is a non-hematological malignancy.

71. The method according to claim 70 wherein said disorder is colon cancer, pancreatic cancer or lymphoma.

72. The method according to claim 67 wherein said disorder is psoriasis or rheumatoid arthritis.

73. The method according to claim 67 wherein said disorder is keratoconjuctivitis sicca.

74. The method according to claim 67 wherein said disorder is cardiovascular disease.

75. The method according to claim 67 wherein said hematological malignancy is chronic myelogenous leukemia or anaplastic large cell lymphoma.

76. The method according to claim 65 or 66 wherein said disorder is asthma.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/012824

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04 C07D519/00 A61K31/52 A61P37/06

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)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , WPI Data, PAJ, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 6 313 129 B1 (UCKUN FATIH M ET AL) 6 November 2001 (2001-11-06) cited in the application Abstract; claims; examples.	1-76
A	WO 2004/099204 A (ASTRAZENECA AB; HEMMERLING, MARTIN; KLINGSTEDT, TOMAS) 18 November 2004 (2004-11-18) Abstract; claims; examples.	1-76
X	WO 00/12089 A (MERCK & CO., INC; BILODEAU, MARK, T ; HUNGATE, RANDALL, W ; CUNNINGHAM,) 9 March 2000 (2000-03-09)	37,38, 40,41, 43,44, 46-48, 50,51, 53-76
A	Abstract; claims; examples.	1-36,39, 42,45, 49,52

☐ 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 document but published on or after the international filing date

"L" document which may throw doubts on prionty 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 pnority 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
3 August 2006	11/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV RIJSWIJK Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Weisbrod, T

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Form PCT/ISA/210 (second sheet) (April 2005)

22

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/012824

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1 [X] Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely

Although claims 65-76 are directed to a method of treatment of the human/am mal body, the search has been carried out and based on the alleged effects of the compound/composition.

2 [ ] Claims Nos
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out specifically

3 [ ] Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 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

Information on patent family members

International application No
PCT/US2006/012824

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6313129 B1	06-11-2001	US 2001044442 A1	22-11-2001
WO 2004099204 A	18-11-2004	AU 2004236144 A1	18-11-2004
		BR PI0410081 A	16-05-2006
		CA 2524624 A1	18-11-2004
		EP 1625126 A1	15-02-2006
		MX PA05012025 A	03-02-2006
WO 0012089 A	09-03-2000	AU 760020 B2	08-05-2003
		AU 3078999 A	21-03-2000
		CA 2341409 A1	09-03-2000
		EP 1109555 A1	27-06-2001
		JP 2002523459 T	30-07-2002

105370

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

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Oficina Internacional

(43) Fecha de Publicación Internacional
12 de octubre de 2006 (12.10.2006)

PCT

(10) Número de Publicación Internacional
WO 2006/108103 A1

(51) Clasificación Internacional de Patentes[7]:
C07D 471/04 (2006.01) *A61K 31/52* (2006.01)
C07D 487/04 (2006.01) *A61P 37/06* (2006.01)
C07D 519/00 (2006.01)

(21) No. Solicitud Internacional: PCT/US2006/012824

(22) Fecha de Presentación Internacional:
5 de abril de 2006 (05.04.2006)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Datos relativos a la Prioridad:
60/668,286 5 de abril de 2005 (05.04.2005) US
60/736,663 15 de noviembre de 2005 (15.11.2005) US

(71) Solicitante *(para todos los países destinatarios con excepción de US)*: **PHARMACOPEIA DRUG DISCOVERY, INC.** [US/US]; 3000 Eastpark Blvd., Cranbury, New Jersey 08512 (US).

(72) Inventores, e
(75) Inventores/Solicitantes *(para US únicamente)*: **OHLMEYER, Michael** [GB/US]; 6 Beechtree Lane, Plainsboro, New Jersey 08536 (US). **BOHNSTEDT, Adolph** [US/US]; 5 Red Fox Street, Burlington, New Jersey 08016 (US). **KINGSBURY, Celia** [NZ/US]; 1 Woodland Avenue, Cream Ridge, New Jersey 08514 (US). **HO, Koc-Kan** [US/US]; 104 Pheasant Run, Monmouth Junction, New Jersey 08852 (US). **QUINTERO, Jorge** [US/US]; 7 Van Delft Drive, South Amboy, New Jersey 08879 (US). **YOU, Ming** [CN/US]; 3 Madison Drive, Plainsboro, New Jersey 08536 (US). **PARK, Haengsoon** [KR/US]; 8910 Tamarron Drive, Plainsboro, New Jersey 08536 (US). **LU, Yingchun** [CN/US]; 91 Stillwell Road, Kendall Park, New Jersey 08824 (US).

(74) Agentes: **HANSEN, Philip** et al.; Heslin Rothenberg Farley & Mesiti P.C., 5 Columbia Circle, Albany, New York 12203 (US).

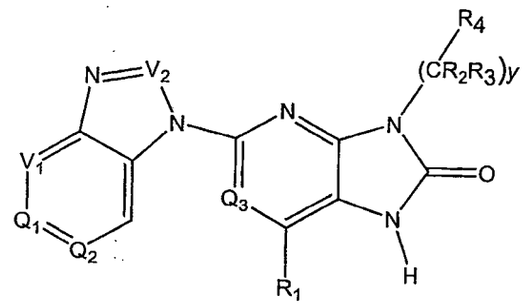
(81) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,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

(84) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

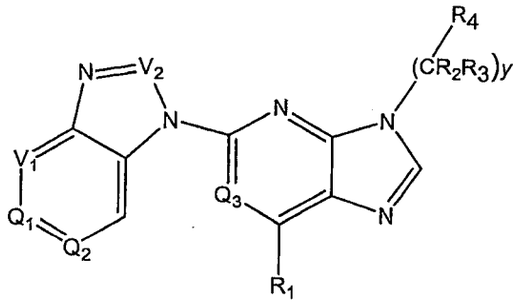
Publicado:
— *sin informe internacional de búsqueda*

[Continúa en la página siguiente]

(54) Título: DERIVADOS DE PURINA E IMIDAZOPIRIDINA PARA INMUNOSUPRESIÓN



(I)



(II)

(57) Extracto: La presente invención proporciona derivados novedosos de purina e imidazopiridina útiles para la prevención y tratamiento de enfermedades autoinmunitarias, enfermedad inflamatoria, enfermedad mediada por mastocitos y rechazo de transplantes. Los compuestos son de las fórmulas generales (I) y (II).

WO 2006/108103 A1

— *antes del vencimiento del tiempo límite para modificar las reivindicaciones y para volverse a publicar en el caso de recibo de modificaciones*

Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

DERIVADOS DE PURINA E IMIDAZOPIRIDINA PARA INMUNOSUPRESIÓN

CAMPO DE LA INVENCIÓN

[0001] La invención se refiere a derivados de purina e imidazopiridina útiles como inmunosupresores.

ANTECEDENTES DE LA INVENCIÓN

[0002] La inmunosupresión es un enfoque clínico importante en tratar la enfermedad autoinmunitaria y en prevenir el rechazo de órganos y tejidos. Los inmunosupresores clínicamente disponibles, incluidos azatioprina, ciclosporina y tacrolimus, aunque efectivos, a menudo ocasionan efectos secundarios indeseables, incluidos nefrotoxicidad, hipertensión, alteraciones gastrointestinales e inflamación de las encías. Los inhibidores de la tirosina cinasa Jak3 son conocidos por ser útiles como inmunosupresores (véase la Patente de los Estados Unidos 6,313,129).

[0003] Los miembros de la familia de cinasas Janus (Jak) de las tirosina cinasas intracelulares de no receptor son componentes de la transducción de señales de citocina. Hasta la fecha se han identificado cuatro miembros de la familia: Jak1, Jak2, Jak3 y Tyk2. Las Jaks juegan un papel clave en la señalización intracelular mediada por receptores de citocina. Luego de la unión de citocinas a sus receptores, las Jaks se activan y fosforilan los receptores, creando sitios de anclaje para otras moléculas señalizadoras, en particular miembros de la familia de transductores y activadores de señales de transcripción (STAT – ***signal transducer and activator of transcription***). Aunque la expresión de Jak1, Jak2 y Tyk2 es relativamente ubicua, la expresión de Jak3 se regula temporal y espacialmente. Jak3 se expresa predominantemente en células de linaje hematopoyético; se expresa constitutivamente en linfocitos citolíticos naturales (NK) y timocitos y es

inducible en linfocitos T, linfocitos B y células mieloides (reseñado en Ortmann, et al, 1999 y Yamaoka, et al., 2004). Jak3 se expresa asimismo en mastocitos, y su actividad enzimática se incrementa por enlazamiento cruzado del receptor IgE/FcεRI (Malaviya y Uckun, 1999).

[0004] Se ha demostrado que un inhibidor de Jak3 específico, oralmente activo, CP-690,550, actúa como un inmunosupresor efectivo y prolonga la supervivencia animal en un modelo murino de transplante de corazón y en un modelo primate de transplante de riñón (Changelian, et al., 2003).

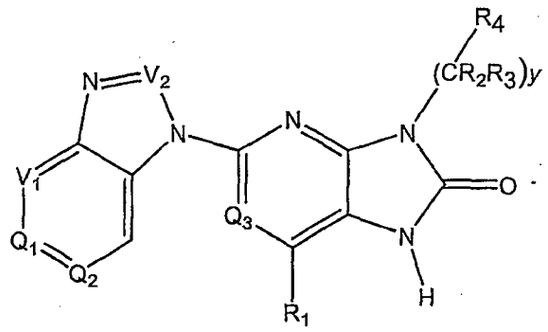
[0005] Más aún, la actividad Jak3 aberrante se ha asociado con una forma leucémica de linfoma de linfocitos T cutáneo (síndrome de Sezary) y leucemia linfoblástica aguda (ALL), la forma más común de cáncer de la niñez. La identificación de inhibidores de Jak3 ha proporcionado la base para nuevos enfoques clínicos en el tratamiento de leucemias y linfomas (Cetkovic-Cvrlje, Marina; Uckun, Faith M., Targeting Janus Kinase 3 in the treatment of Leukemia and hiflammatory Diseases. Archivum Immunologiae et Therapie Experimentalis (2004) y/o Uckun, Faith M.; Mao, Chen. Tyrosine kinases as new molecular targets in treatment of inflammatory disorders and leukemia. Current Parmaceutical Design(2004)). Se ha divulgado que dos derivados de dimetoxiquinazolina, WH1-P131 (JANEX-1) y WHI-P154 (JANEX-2) son inhibidores selectivos de Jak3 en células de leucemia (Sudbeck et al., 1999).

[0006] Se ha demostrado asimismo que Jak3 juega un papel en reacciones alérgicas mediadas por mastocitos y enfermedades inflamatorias y sirve como diana en indicaciones tales como asma y anafilaxia.

[0007] En consecuencia, compuestos que inhiben Jak3 son útiles para indicaciones tales como leucemias y linfomas, rechazo de trasplante de órganos y médula espinal, reacciones alérgicas mediadas por mastocitos y enfermedades y trastornos inflamatorios.

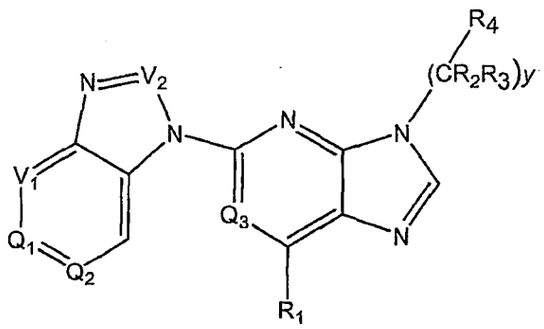
SUMARIO DE LA INVENCIÓN

[0008] Se ha descubierto ahora que compuestos de la fórmula general I y II son inhibidores potentes y selectivos de Jak3:



I

y



II

[0009] En estos compuestos,

Q_1 y Q_2 se seleccionan independientemente del grupo conformado por CX_1, CX_2, y nitrógeno;

Q_3 es N o CH;

X_1 y X_2 se seleccionan independientemente del grupo conformado por hidrógeno, $(C_1\text{-}C_6)$alquilo, ciano, halo, halo$(C_1\text{-}C_6)$alquilo, hidroxilo, $(C_1\text{-}C_6)$alcoxi, halo$(C_1\text{-}C_6)$alcoxi, nitro, carboxamido, y metilsulfonilo;

V_1 y V_2 se seleccionan independientemente de CH y N;

R_1 se selecciona del grupo conformado por hidrógeno y metilo;

y es cero o un entero seleccionado de 1, 2 y 3;

R_2 y R_3 se seleccionan independientemente para cada ocurrencia de (CR_2R_3) del grupo conformado por hidrógeno y $(C_1\text{-}C_6)$alquilo; y

R_4 se selecciona de un grupo conformado por alquilo, heterociclilo, aril, alquilo sustituido, heterociclilo sustituido, y arilo sustituido.

[0010] Los miembros de estos géneros son útiles en inhibir la actividad Jak3 y, como tales, son útiles en indicaciones donde se desea la inmunosupresión clínical y en el tratamiento de neoplasias malignas hematológicasγ.

[0011] En otro aspecto, la invención se refiere a composiciones farmacéuticas que comprenden una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula general I o fórmula general II, o su sal farmacéuticamente aceptable; y una sustancia portadora farmacéuticamente aceptable.

[0012] En otro aspecto, la invención se refiere a un método para tratar una enfermedad alterando una respuesta mediada por la tirosina cinasa Jak3. El método comprende poner en contacto con Jak3 por lo menos un compuesto de la fórmula general I ó II.

[0013] En todavía otro aspecto, la presente invención se refiere a un método de suprimir el sistema inmunitario en un sujeto necesitado de ello, que comprende administrar al sujeto una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula general I ó II.

[0014] La supresión de la actividad del sistema inmunitario es deseable para prevenir o tratar rechazo de órganos o tejidos luego de la cirugía de transplante y para prevenir y tratar enfermedades y trastornos originados en la actividad aberrante del sistema inmunitario, en particular trastornos y enfermedades autoinmunitarias. Trastornos autoinmunitarios ejemplares incluyen enfermedad del injerto contra el anfitrión (GVHD, por sus siglas en inglés), diabetes insulinodependiente (tipo I), tiroiditis de Hashimoto y enfermedad de Graves, anemia perniciosa, enfermedad de Addison,

hepatitis activa crónica, enfermedad de Crohn, colitis ulcerosa, artritis reumatoide, esclerosis múltiple, lupus sistémico eritematoso, psoriasis, escleroderma y miastenia grave.

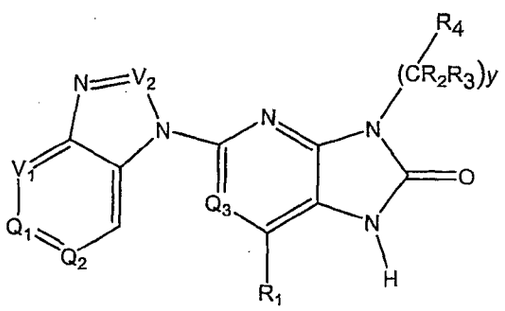
[0015] Los compuestos de la presente invención son útiles en prevenir y tratar enfermedades y trastornos relacionados con reacciones alérgicas e inflamación mediadas por mastocitos.

[0016] Otras indicaciones en las cuales son útiles los inhibidores de Jak3 incluyen leucemias y linfomas.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0017] A todo lo largo de esta especificación los sutituyentes se definen cuando se introducen y conservan sus definiciones.

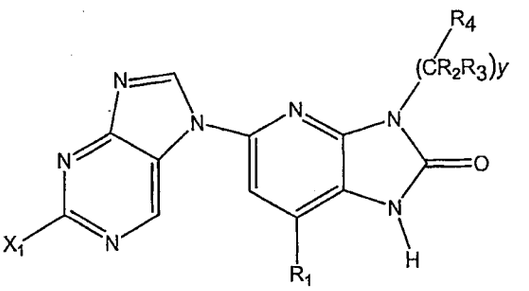
[0018] En un primer aspecto la invención se refiere a purinonas e imidazopiridinonas que tienen la fórmula general I:

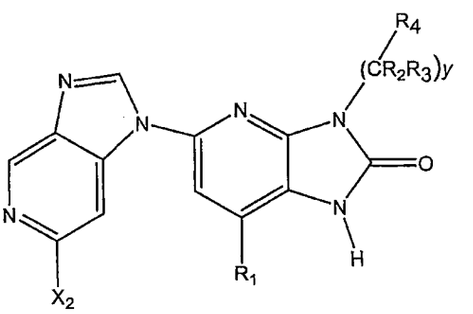


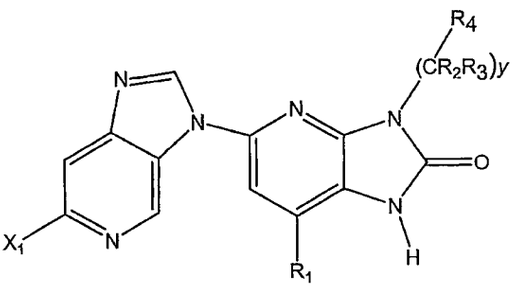
I

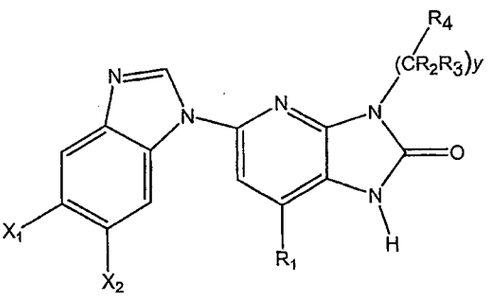
[0019] Los miembros del género I pueden dividirse convenientemente en subgéneros basados en los valores de Q y V. Cuando Q_1 es carbono, Q_2 es nitrógeno, V_1 es nitrógeno, y V_2 es carbono, surge un subgénero de purinonas e imidazo[4,5-b]piridinonas que tienen una purina enlazada. Cuando Q_1 es carbono, Q_2 es nitrógeno, y los dos V_1 y V_2 son carbono, surge un subgénero de purinonas e imidazo[4,5-b]piridinonas que tienen una imidazo[5,4-c]piridina enlazada. Cuando Q_1 y Q_2 son carbono, y los

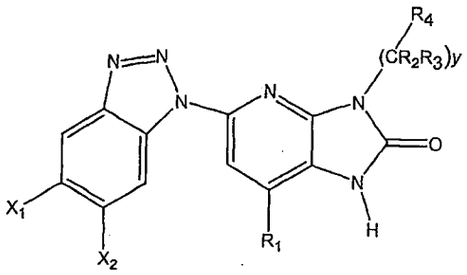
dos V_1 y V_2 son carbono, surge un subgénero de purinonas e imidazo[4,5-b]piridinonas que tiene un benzimidazol enlazado. Cuando Q_1 y Q_2 son carbono, V_1 es carbono, y V_2 es nitrógeno, surge un subgénero de purinonas e imidazo[4,5-b]piridinonas que tiene un benzotriazol enlazado. El género podría dividirse análogamente sobre la base de Q_3. Cuando Q_3 es nitrógeno, surge un subgénero de purinonas que tienen una purina, imidazo[5,4-c]piridina, benzimidazol o benzotriazol enlazado. Cuando Q_3 es carbono, surge un subgénero de imidazo[4,5-b]piridinonas que tienen una purina, imidazo[5,4-c]piridina, benzimidazol o benzotriazol enlazado. Las estructuras de estos subgéneros se indican a continuación:



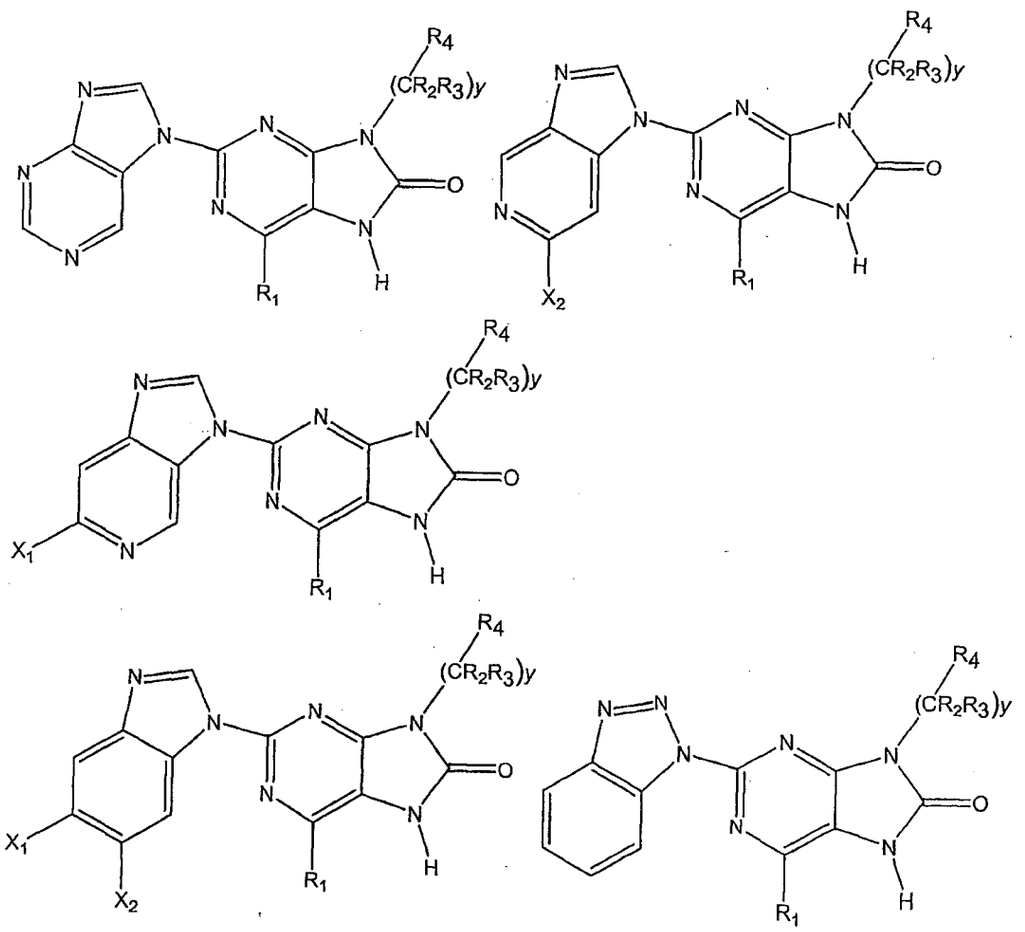




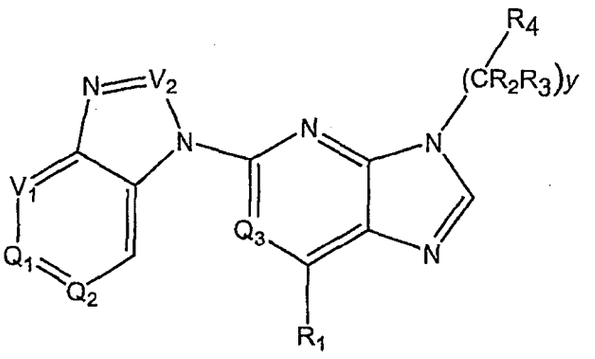




[0020] Cuando Q_3 es nitrógeno, surge un subgénero de purinonas que tienen una purina, imidazo[5,4-c]piridina, benzimidazol o benzotriazol enlazado. Las estructuras de estos subgéneros se indican a continuación

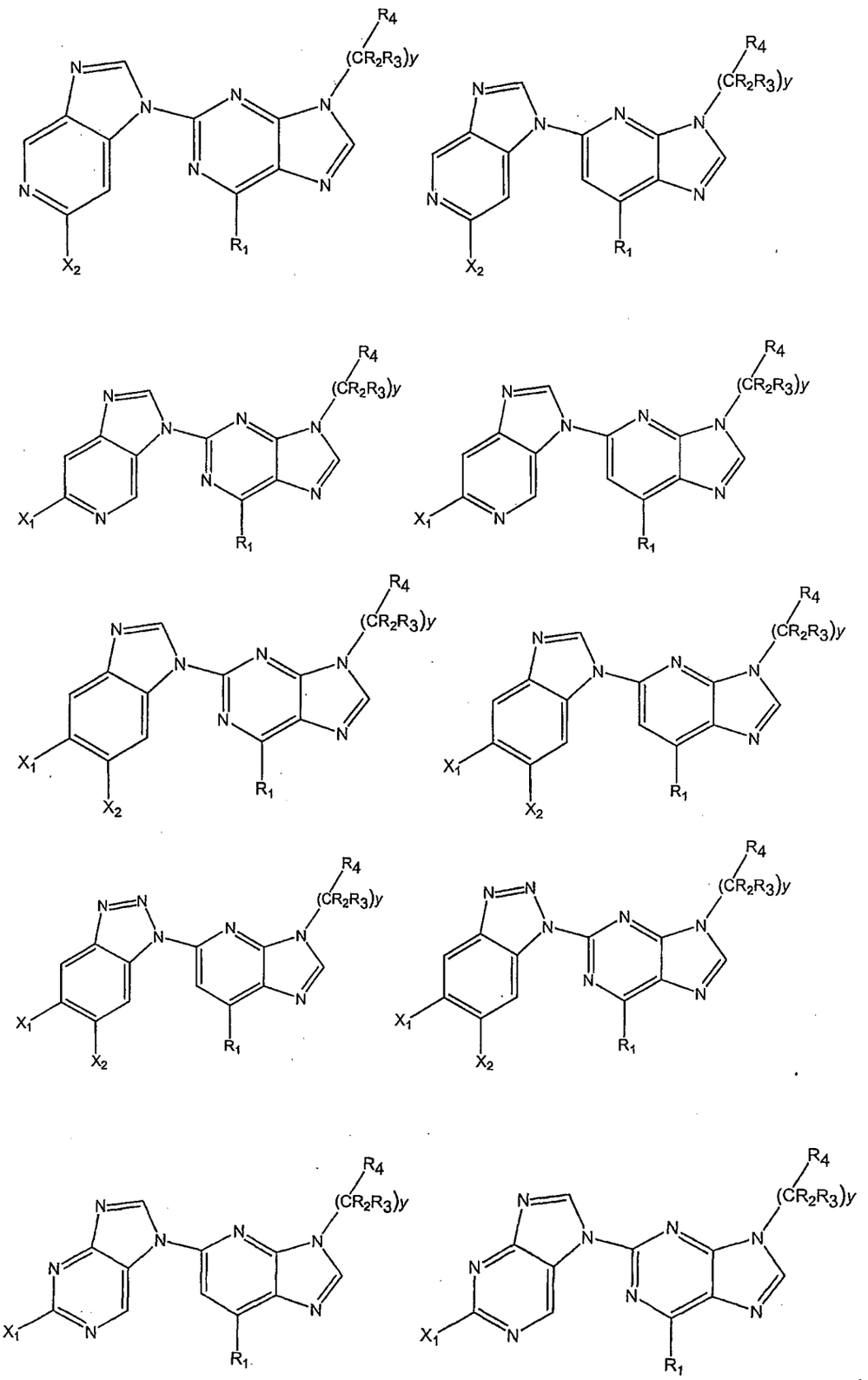


[0021] En otro aspecto la invención se refiere a purinas e imidazopiridinas que tienen la fórmula general **II**:



II

[0022] Igualmente los miembros del género II pueden dividirse en subgéneros basados en los valores de Q y V. Cuando Q_1 es carbono, Q_2 es nitrógeno, V_1 es nitrógeno, y V_2 es carbono, surge un subgénero de purinas e imidazo[4,5-b]piridinas que tienen una purina enlazada. Cuando Q_1 es carbono, Q_2 es nitrógeno, y los V_1 y V_2 son carbono, surge un subgénero de purinas e imidazo[4,5-b]piridinas que tiene una imidazo[5,4-c]piridina enlazada. Cuando todos Q_1, Q_2, V_1 y V_2 son carbono, surge un subgénero de purinas e imidazo[4,5-b]piridinas que tiene un benzimidazol enlazado. Cuando Q_1, Q_2 y V_1 son carbono, y V_2 es nitrógeno, surge un subgénero de purinas e imidazo[4,5-b]piridinas que tienen un benzotriazol enlazado. Análogamente el género podría dividirse sobre la base de Q_3. Cuando Q_3 es nitrógeno, surge un subgénero de purinas que tienen una purina, imidazo[5,4-c]piridina, benzimidazol o benzotriazol enlazados. Cuando Q_3 es carbono, surge un subgénero de imidazo[4,5-b]piridinas que tienen una purina, imidazo[5,4-c]piridina, benzimidazol o benzotriazol enlazados. Les estructuras de estos subgéneros se muestran a continuación:

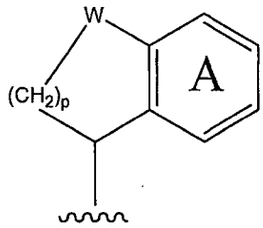


[0023] En ciertas incorporaciones, X_1 y X_2 se seleccionan de hidrógeno, ciano, cloro, fluoro, trifluorometilo, trifluorometoxi, carboxamido, y metilo; en otras incorporaciones R_1 es H. En una subdivisión, y es cero; en otra, y es 1 ó 2 y R_2 y R_3 son hidrógeno o metilo. Ejemplos de R_4 incluyen: ciclopentilo, ciclohexilo, piperidina, oxepano, benzoxepano,

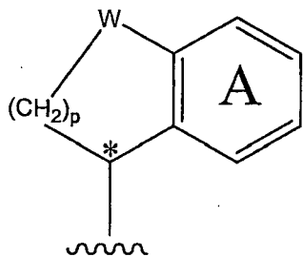
dihidrociclopentapiridina, fenilo, tetralina, indano, tetrahidropirano, tetrahidrofurano, tetrahidroindol, isoquinolina, tetrahidroisoquinolina, quinolina, tetrahidroquinolina, cromano, isocromano, piridina, pirazina, pirimidina, dihidropirano, dihidrobenzofurano, tetrahidrobenzofurano, tetrahidrobenzotiofeno, furano, dihidropirano[2,3-b]piridina (véase ejemplo más adelante), tetrahidroquinoxalina, tetrahidrotiopirano (tiano), tiocromano (dihidrobenzotiína), tiocroman-1,1-dióxido, tetrahidronaftaleno, oxabiciclooctano, oxocano, tetratiohidropiran-1,1-dióxido, tetratiohidropiranóxido, o cualquiera de los anillos anteriores que lleven de 1-3 sustituyentes adicionales, tales como halógeno, metilo, metoxi, trifluorometilo, ciano, hidroxi, oxo, óxido y acetilo. Ejemplos adicionales en los cuales R_4 es alquilo o alquilo sustituido incluyen subgéneros en los cuales R_4 es oxaalquilo (alcoxialquilo).

[0024] En ciertas incorporaciones del género **I**, **y** es 1 ó 2; R_2 y R_3 son hidrógeno o metilo y R_4 es fenilo, quinolina, piridina, pirazina o fenilo sustituido, quinolina, piridina o pirazina. En otras incorporaciones del género **I**, **y** es cero y R_4 es ciclopentilo, ciclohexilo, fenilo, piperidina, oxepano, benzoxepano, dihidrociclopentapiridina, tetralina, indano, tetrahidropirano, tetrahidrofurano, tetrahidroindol, isoquinolina, tetrahidroisoquinolina, quinolina, tetrahidroquinolina, cromano, piridina, pirimidina, dihidropirano, dihidrobenzofurano, tetrahidrobenzofurano, tetrahidrobenzotiofeno, dihidrobenzotiofeno, furano, dihidropirano[2,3-b]piridina, tetrahidroquinoxalina, tetrahidrothiopirano (tiano), tiocromano (dihidrobenzotiína), tiocroman-1,1-dióxido, tetrahidronaftaleno, oxabiciclooctano, oxocano, tetrathiohidropiran-1,1-dióxido, tetrathiohidropiranóxido, o un anillo sustituido del listado anterior. En incorporaciones adicionales, (a) **y** es cero y R_4 se selecciona de ciclopentilo, ciclohexilo, oxepano, dihidrociclopentapiridina, tetrahidropirano, tetrahidroquinolina, cromano, dihidrobenzofurano, tetrahidrobenzofurano, dihidropirano[2,3-b]piridina y tetrahidroquinoxalina, sustituido cada uno opcionalmente con hidroxi, oxo, o halógeno; o (b) **y** es 1 ó 2, R_2 y R_3 son

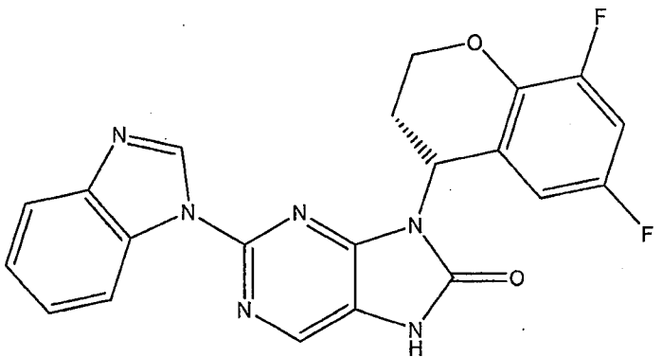
hidrógeno o metilo y R_4 se selecciona de fenilo, piridina y pirazina, sustituido cada uno opcionalmente con halógeno. Cuando **y** es cero, R_4 puede ser tetrahidropiran-4-ilo, 4-hidroxiciclohexilo, 4-oxociclohexilo, oxepan-4-ilo, croman-4-ilo o croman-4-ilo fluoro sustituido. Parece que, aunque ambos enantiómeros son activos, los compuestos en los cuales el carbono en [la posición] 4 del cromano es de la configuración (R) tienen una potencia mayor. Algunos de los subgéneros anteriores en los cuales **y** es cero pueden describirse igualmente por una representación en la cual R_4 es



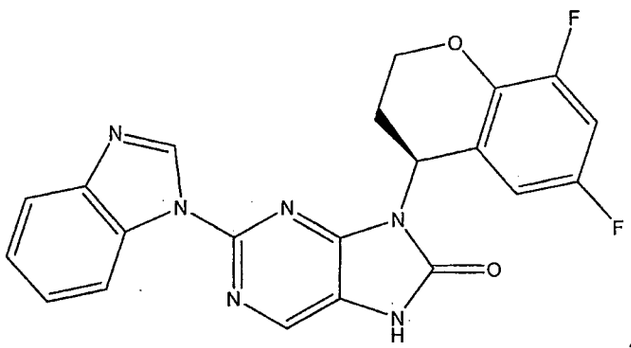
[0025] De acuerdo con esta representación, W es CH_2, C=O, CHOH, u O; p es 1, 2 ó 3; y A es un anillo heteroaromático de seis miembros que contiene 1 ó 2 nitrógenos, un anillo benceno sustituido opcionalmente con uno o dos flúoros, o un anillo heterocíclico de cinco miembros. La línea ondulada denota el punto de enlace a la purinona. Ejemplos en los cuales W es C=O incluyen indanonas, tetralonas y benzosuberonas. Ejemplos en los cuales W es CH_2 incluyen indanos, tetralinas y benzocicloheptanos. Ejemplos en los cuales W es CHOH incluyen tetralinas sustituidas. Ejemplos en los cuales W es O incluyen dihidrobenzofurano, cromano, benzopiranos y benzoxepanos. Como anteriormente, los compuestos en los cuales el carbono marcado con un asterisco



es de la configuración (R) parecen ser más potentes que sus correspondientes (S) enantiómeros. Un ejemplo de tal compuesto es



el cual es más potente que su correspondiente (S) enantiómero



pero ambos exhiben una IC_{50} de la cinasa Jak3 por debajo de 1 micromolar. Los ejemplos siguientes incluyen asimismo compuestos en los cuales **y** es 1 y R_4 se selecciona de difluorofenilo, fluorofenilo, chlorofenilo, chlorofluorofenilo, piridin-3-ilo y pirazin-3-ilo.

[0026] En ciertas incorporaciones del género **II**, el nitrógeno está presenten la posición 7 y 9 en el heterociclo 6,5 bicíclico; X_1 se selecciona de hidrógeno, ciano y fluoro; Q_1 es N y R_1 es H. En algunas incorporaciones, **y** es cero y R_4 se selecciona de fenilo, tetrahidropirano (por ejemplo, tetrahidropiran-4-ilo), isoquinolina (por ejemplo, isoquinolin-8-ilo), tetrahidroquinolina (por ejemplo, 1,2,3,4-tetrahidroquinolin-5-ilo), y sus contrapartes sustituidas. En otras incorporaciones, **y** es 1 y R_4 se selecciona de difluorofenilo, fluorofenilo, clorofenilo, clorofluorofenilo, piridin-3-ilo y pirazin-3-ilo.

[0027] Todos los compuestos que caen dentro de los anteriores géneros originales y sus subgéneros con útiles como inhibidores de Jak3.

Definiciones

[0028] Para conveniencia y claridad se describen aquí ciertos términos empleados en la especificación, ejemplos y reivindicaciones.

[0029] Alquilo tiene por objeto incluir estructuras de hidrocarburo lineales, ramificadas o cíclicas y sus combinaciones. Alquilo inferior se refiere a grupos alquilo de desde 1 a 6 átomos de carbono. Ejemplos de grupos alquilo inferior incluyen metilo, etilo, propilo, isopropilo, butilo, s- y t-butilo y similares. Grupos alquilo preferidos son aquellos de C_{20} o menos; más preferidos son C_1-C_8 alquilo. Cicloalquilo es un subconjunto de alquilo e incluye grupos hidrocarburo cíclicos de desde 3 a 8 átomos de carbono. Ejemplos de grupos cicloalquilo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, norbornilo, u otros sistemas puenteados y similares.

[0030] C_1 a C_{20} hidrocarburo incluye alquilo, cicloalquilo, alquenilo, alquinilo, arilo y sus combinaciones. Ejemplos incluyen fenetilo, ciclohexilmetilo, canforilo y naftiletilo.

[0031] Alcoxi o alcoxilo se refiere a grupos de desde 1 a 8 átomos de carbono de una configuración cíclica, recta, ramificada y sus combinaciones unidas a la estructura original mediante un oxígeno. Ejemplos incluyen metoxi, etoxi, propoxi, isopropoxi, ciclopropiloxi, ciclohexiloxi y similares. Alcoxi inferior se refiere a grupos que contienen 1 a 4 carbonos. Oxaalquilo se refiere a residuos alquilo en los cuales uno o más carbonos (y sus hidrógenos asociados) se han reemplazado por oxígeno. Ejemplos incluyen metoxipropoxi, 3,6,9-trioxadecilo y similares. El término oxaalquilo tiene por objeto entenderse como tal en el arte [véase Naming and Indexing of Chemical Substances for Chemical Abstracts, publicado por the American Chemical Society, 196, pero sin la restricción de 127(a)], es decir, se refiere a compuestos en los cuales el oxígeno se une mediante un enlace único a

sus átomos adyacentes (formando enlaces éter); no se refiere a oxígeno de doble enlace, como se encontraría en grupos carbonilo.

[0032] Acilo se refiere a grupos de desde 1 a 8 átomos de carbono de una configuración cíclica, recta, ramificada, saturada, insaturada y aromática y sus combinaciones, unidos a la estructura original a través de una funcionalidad carbonilo. Uno o más carbonos en el residuo acilo pueden reemplazarse por nitrógeno, oxígeno o azufre, siempre que el punto de enlace al original permanezca en el carbonilo. Ejemplos incluyen acetilo, benzoilo, propionilo, isobutirilo, t-butoxicarbonilo, benciloxicarbonilo y similares. Acilo inferior se refiere a grupos que contienen uno a cuatro carbonos.

[0033] Arilo y heteroarilo significan un anillo aromático o heteroaromático de 5 ó 6 miembros, que contiene 0-3 heteroátomos seleccionados de O, N, o S; un sistema de anillo aromático o heteroaromático de 9 ó 10 miembros, bicíclico, que contiene 0-3 heteroátomos seleccionados de O, N, o S; o un sistema de anillo aromático o heteroaromático de 13 ó 14 miembros, tricíclico, que contiene 0-3 heteroátomos seleccionados de O, N, o S. Los anillos carbocíclicos de 6 a 14 miembros, aromáticos, incluyen, por ejemplo, benceno y naftaleno, y para los propósitos de la presente invención, fracciones fusionadas tales como tetrahidronaftaleno (tetralina), e indano, en las cuales uno o más anillos son aromáticos, pero no todos necesitan serlo. Los anillos heterocíclicos aromáticos de 5 a 10 miembros incluyen, por ejemplo,, imidazol, piridina, indol, tiofeno, benzopiranona, tiazol, furano, benzimidazol, quinolina, isoquinolina, quinoxalina, pirimidina, pirazina, tetrazol y pirazol.

[0034] Arilalquilo se refiere a un sustituyente en el cual un residuo arilo se enlaza a la estructura original a través de alquilo. Ejemplos son bencilo, fenetilo y similares. Heteroarilalquilo se refiere a un sustituyente en el cual

un residuo heteroarilo se enlaza a la estructura original a través de alquilo. Ejemplos incluyen, por ejemplo, piridinilmetilo, pirimidiniletilo y similares.

[0035] Heterociclo significa un residuo arilo en el cual de uno a tres carbonos se reemplazan por un heteroátomo seleccionado del grupo conformado por N, O y S. Los heteroátomos de nitrógeno y azufre pueden oxidarse en forma opcional, y el heteroátomo de nitrógeno puede cuaternizarse en forma opcional. Ejemplos de heterociclos incluyen pirrolidina, pirazol, pirrol, indol, quinolina, isoquinolina, tetrahidroisoquinolina, benzofurano, benzodioxano, benzodioxol (comúnmente conocido como metilendioxifenilo, cuando ocurre como un sustituyente), tetrazol, morfolina, tiazol, pirazina, piridina, piridazina, pirimidina, tiofeno, furano, oxazol, oxazolina, isoxazol, dioxano, tetrahidrofurano y similares. Otros ejemplos incluyen éteres cíclicos (incluidos éteres cíclicos puenteados), lactonas, lactamas, úreas cíclicas, y similares. Hay que anotar que heteroarilo es un subconjunto de heterociclo en el cual el heterociclo es aromático. Ejemplos de residuos heterociclilo incluyen adicionalmente piperazinilo, 2-oxopiperazinilo, 2- oxopiperidinilo, 2-oxo-pirrolidinilo, 2-oxoazepinilo, azepinilo, 4-piperidinilo, pirazolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazinilo, oxazolidinilo, isoxazolidinilo, tiazolidinilo, isotiazolilo, quinuclidinilo, isotiazolidinilo, benzimidazolilo, tiadiazolilo, benzopiranilo, benzotiazolilo, tetrahidrofurilo, tetrahidropiranilo, tienilo, benzotienilo, tiamorfolinilo, tiamorfolinilsulfóxido, tiamorfolinilsulfona, oxadiazolilo, triazolilo y tetrahidroquinolinilo. Un heterociclo de nitrógeno es un heterociclo que contiene por lo menos un nitrógeno en el anillo; puede contener nitrógenos adicionales, así como otros heteroátomos. El heterociclo de nitrógeno puede ser monocíclico, bicíclico, o multi-cíclico.

[0036] Alquilo, arilo, cicloalquilo, heterociclilo sustituido, etc., se refieren a alquilo, arilo, cicloalquilo, o heterociclilo en donde hasta tres átomos H en cada residuo se reemplazan con halógeno, haloalquilo, hidroxi, alcoxi

inferior, hidroxialquilo inferior, carboxi, carboalcoxi (también conocido como alcoxicarbonilo), carboxamido (también conocido como alquilaminocarbonilo), ciano, carbonilo, nitro, amino, alquilamino, dialquilamino, mercapto, alquiltio, sulfóxido, sulfona, acilamino, amidino, fenilo, bencilo, heteroarilo, fenoxi, bencenosulfonilo, benciloxi, o heteroariloxi. Cuando el original es una heterociclo que permite tal sustitución, el término incluye asimismo óxidos, por ejemplo piridin-N-óxido, tiopiran sulfóxido y tiopiran- S,S-dióxido. Como se mencionó anteriormente, dos hidrógenos en un solo carbono puede reemplazarse por un carbonilo para formar un derivado oxo. Residuos arilo oxo-sustituido dignos de mención incluyen tetralona (3,4-dihidronaftalen-1(2*H*)-ona) e indanona (2,3-dihidroinden-1-ona).

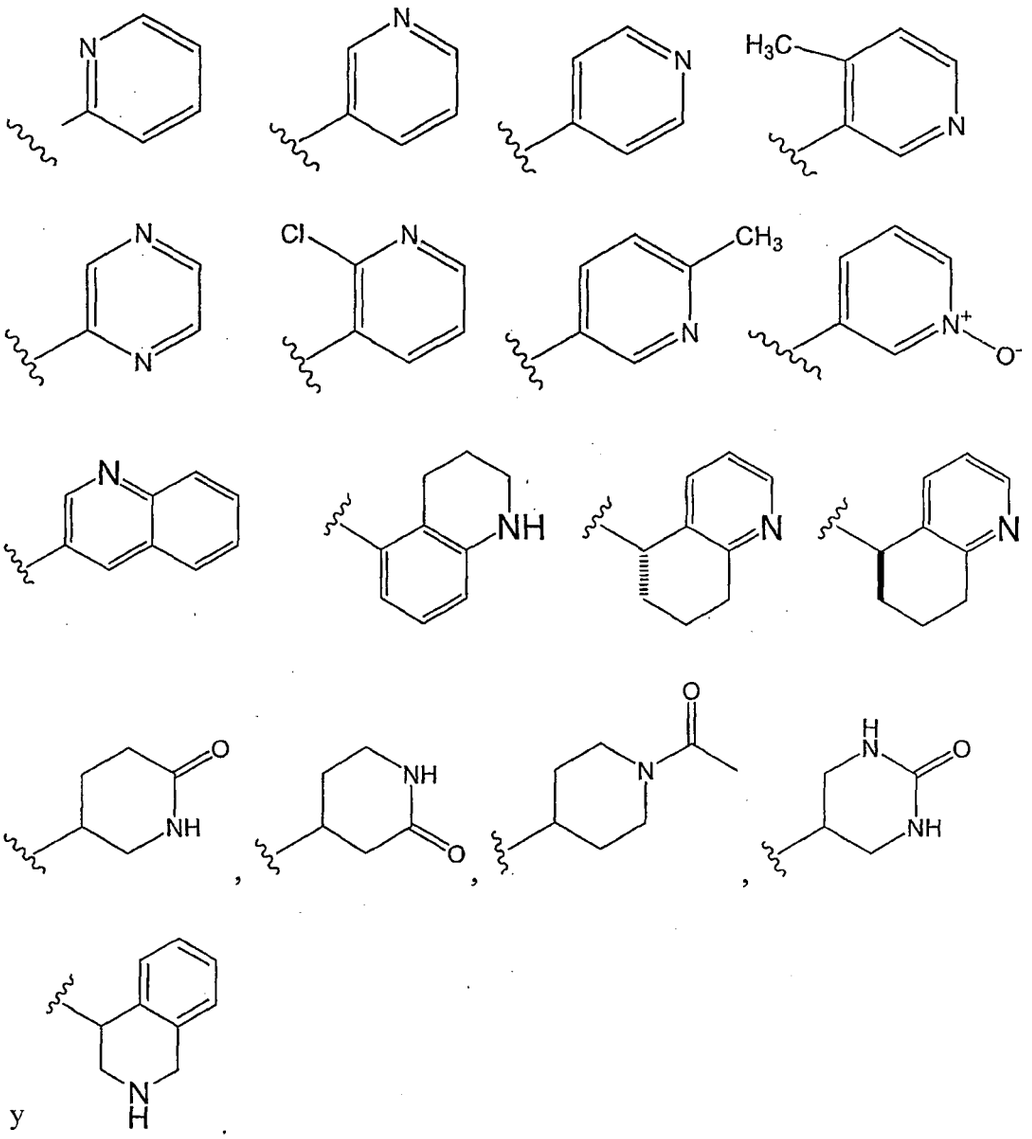
[0037] Los términos "halógeno" y "halo" se refieren a flúor, cloro, bromo o yodo.

[0038] Algunos de los compuestos descritos en esta solicitud pueden contener uno o más centros asimétricos y, en consecuencia, pueden dar origen a enantiómeros, diastereómeros, y otras formas estereoisoméricas que pueden definirse, en términos de estereoquímica absoluta, como (R)- o (S)-. La presente invención pretende incluir la totalidad de dichos posibles isómeros, así como sus formas racémicas y ópticamente puras. (R)- y (S)-isómeros ópticamente activos pueden prepararse usando sintonas quirales o reactivos quirales, o resolverse usando técnicas convencionales. Cuando los compuestos descritos en esta solicitud contienen enlaces dobles olefínicos u otros centros de asimetría geométrica y, a menos que se especifique lo contrario, se pretende que los compuestos incluyan ambos isómeros geométricos E y Z. Análogamente, se pretende que todas las formas tautoméricas estén incluidas. La configuración de cualquier enlace doble carbono-carbono que aparece en esta solicitud se selecciona por conveniencia únicamente y no pretende designar una configuración particular; por lo tanto, un enlace doble carbono-carbono descrito

arbitrariamente en esta solicitud como *trans* puede ser Z, E o una mezcla de los dos en cualquier proporción.

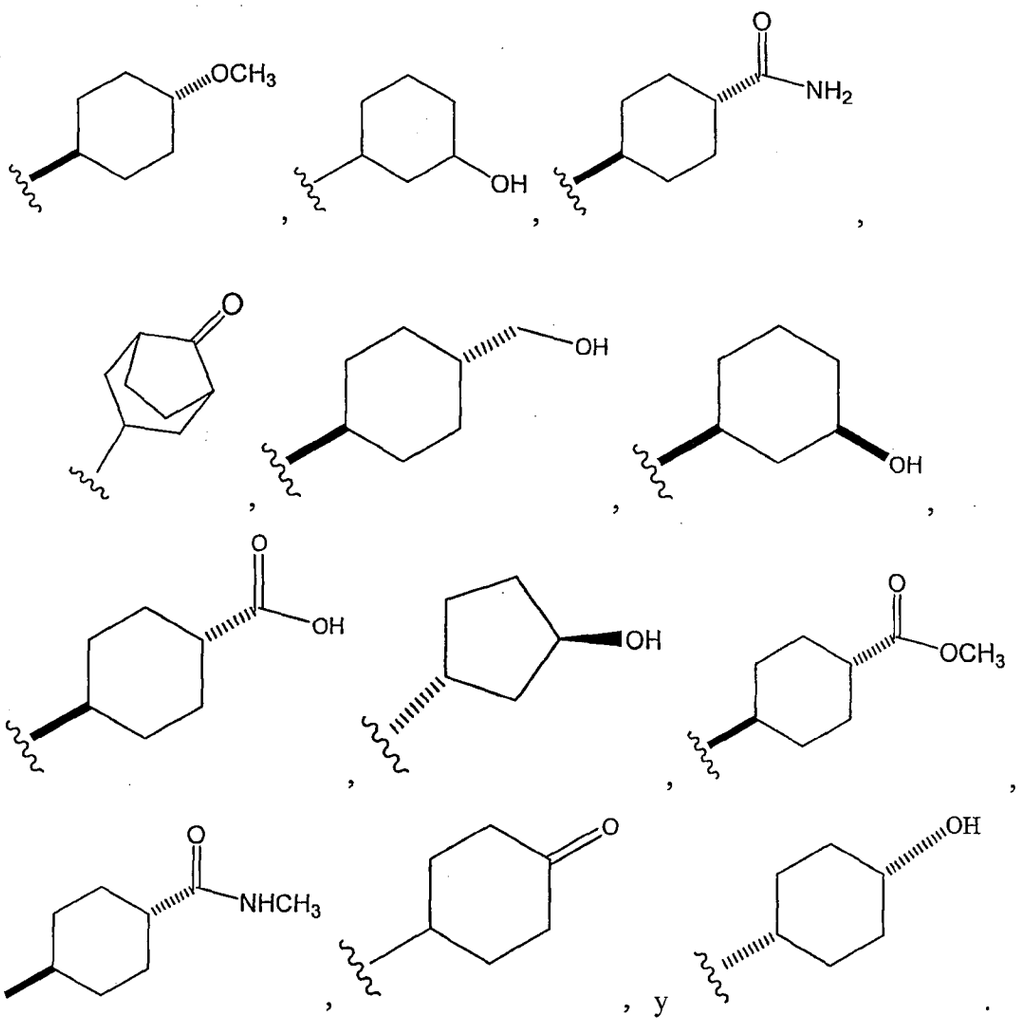
[0039] Se reconocerá que los compuestos de esta invención pueden existir en forma radiomarcada, es decir, los compuestos pueden contener uno o más átomos que contienen una masa atómica o número de masa diferente de la masa atómica o número de masa encontrados usualmente en la naturaleza. Radioisótopos de hidrógeno, carbono, fósforo, flúor, cloro y yodo incluyen ^{3}H, ^{14}C, ^{35}S, ^{18}F, ^{36}Cl y ^{125}I, respectivamente. Compuestos que contienen aquellos radioisótopos y/u otros radioisótopos de otros átomos se encuentran dentro del ámbito de esta invención. Radioisótopos tritiados, es decir ^{3}H, y carbono-14, es decir, ^{14}C, son particularmente preferidos por su comodidad en la preparación y detectabilidad. Compuestos radiomarcados de esta invención pueden prepararse generalmente por métodos bien conocidos por los expertos en el arte. Convenientemente, tales compuestos radiomarcados pueden prepararse llevando a cabo los procedimientos divulgados en los Ejemplos sustituyendo un reactivo radiomarcado fácilmente disponible por un reactivo no radiomarcado. Debido a la alta afinidad para el sitio activo de la enzima JAK3, compuestos radiomarcados de la invención son útiles para análisis de JAK3.

[0040] En una incorporación, R_4 es un heterociclo seleccionado de un heterociclo de nitrógeno y un heterociclo de oxígeno. Heterociclos de nitrógeno que aparecen en los ejemplos son heterociclos monocíclicos y bicíclicos o heterociclos monocíclicos y bicíclicos sustituidos con una o dos sustituciones. Cuando ***y*** no es cero, heteroarilo es un subconjunto preferido de heterociclilo para R_4. Heterociclos de nitrógeno ejemplares incluyen piperidina, piridina, pirazina, pirimidina, piridina, quinolina, isoquinolina, tetrahidroquinolina, tetrahidroisoquinolina, y sus derivados sustituidos en varias formas, tales como

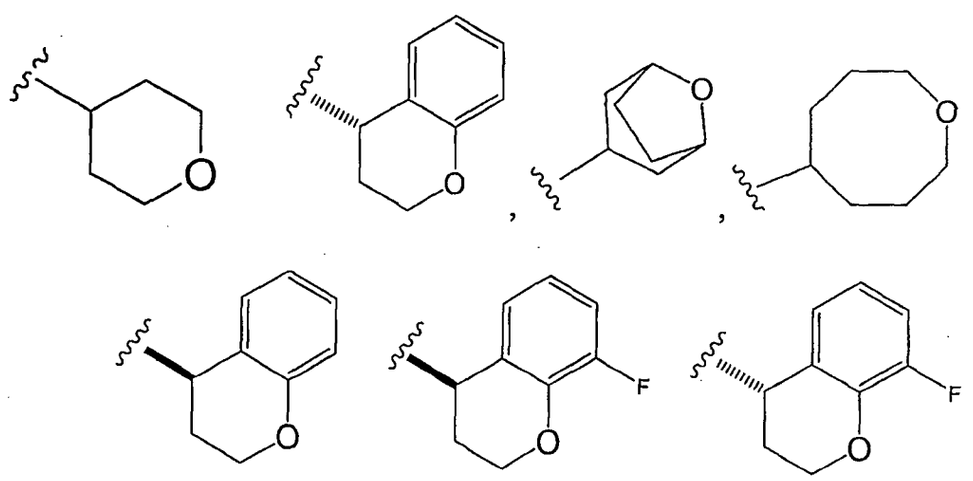


y

[0041] En otra incorporación, R_4 es un cicloalquilo sustituido. Los substituyentes incluyen hidroxilo, alcoxi, hidroxialquilo, oxo, carboxamido (aminocarbonilo), carboxi, y carboalcoxi. Cicloalquilos sustituidos incluyen:



[0042] Un heterociclo de oxígeno es un heterociclo que contiene por lo menos un oxígeno en el anillo; puede contener oxígenos adicionales, así como otros heteroátomos. Heterociclos de oxígeno ejemplares incluyen tetrahidropirano, cromano, pirano, oxocano y sus derivados sustituidos en varias formas, tales como:



Síntesis Química

[0043] La terminología relacionada con funcionalidades de "protector", "desprotector" y "protegido" ocurre a todo lo largo de esta solicitud. Tal terminología es bien entendida por personas expertas en el arte y se utiliza en el contexto de procesos que involucran el tratamiento consecutivo con una serie de reactivos. En ese contexto, un grupo protector se refiere a un grupo que se utiliza para enmascarar una funcionalidad durante un paso del proceso en el cual reaccionaría de otra forma, pero en el cual la reacción es indeseada. El grupo protector impide la reacción en ese paso, pero puede retirarse posteriormente para exponer la funcionalidad original. El retiro o "desprotección" ocurre luego de la consumación de la reacción o reacciones en las cuales interferiría la funcionalidad. Por lo tanto, cuando se especifica una secuencia de reactivos, como se hace en los procesos de la invención, la persona de habilidad ordinaria en el arte puede imaginar fácilmente aquellos grupos que serían apropiados como "grupos protectores". Grupos apropiados para este propósito se discuten en libros de texto estándar en el campo de la química, tales como Protective Groups in Organic Synthesis by T.W. Greene [John Wiley & Sons, New York, 1991], que se incorpora en esta solicitud por referencia.

[0044] Un listado exhaustivo de abreviaturas utilizadas por los químicos orgánicos aparece en la primera edición de cada volumen del Journal of Organic Chemistry. El listado, que se presenta típicamente en una tabla titulada "Standard List of Abbreviations", se incorpora en esta solicitud por referencia.

[0045] En general, los compuestos de la presente invención pueden prepararse por los métodos ilustrados en los esquemas de reacción general como, por ejemplo, se describe más adelante, o mediante modificaciones de los mismos, usando materiales de partida fácilmente disponibles, reactivos y procedimientos de síntesis convencionales. En estas reacciones, es

también posible hacer uso de variantes que son conocidas en sí mismas, pero que no se mencionan aquí. Los materiales de partida, por ejemplo, en el caso de compuestos de anillo benzimidazol apropiadamente sustituido, o bien se encuentran disponibles en el comercio, se sintetizan como se describe en los ejemplos o bien pueden obtenerse por los métodos bien conocidos por personas de habilidad en el arte.

[0046] La presente invención provee además composiciones farmacéuticas que comprenden como agentes activos, los compuestos descritos en esta solicitud.

[0047] Tal como se emplea en esta solicitud una "composición farmacéutica" se refiere a una preparación de uno o más de los compuestos descritos aquí, o sus sales o disolventes fisiológicamente aceptables, con otros componentes químicos tales como sustancias portadoras y excipientes fisiológicamente apropiados.

[0048] En consecuencia, composiciones farmacéuticas para uso de acuerdo con la presente invención pueden formularse de manera convencional usando una o más sustancias portadoras fisiológicamente aceptables incluidos excipientes y auxiliares, que faciliten el procesamiento de los compuestos activos en preparaciones que puedan emplearse farmacéuticamente. La formulación apropiada depende de la vía de administración elegida.

[0049] Compuestos que inhiben Jak-3 pueden formularse como composiciones farmacéuticas y administrarse a un sujeto mamífero, tal como un paciente humano en una variedad de formas adaptadas a la vía de administración elegida, es decir, por vías oral o parenteral, intravenosa, intramuscular, tópica, transdérmica o subcutánea.

[0050] Para administración oral, los compuestos pueden formularse fácilmente combinando los compuestos activos con sustancias portadoras farmacéuticamente aceptables, bien conocidos en el arte. Tales sustancias portadoras permiten formular los compuestos de la invención como tabletas, píldoras, grageas, cápsulas, líquidos, geles, jarabes, mezclas líquidas, suspensiones, y similares, para ingestión oral por un paciente. Preparaciones farmacológicas para uso oral pueden elaborarse usando un excipiente sólido, moliendo opcionalmente la mezcla resultante, y procesando la mezcla de gránulos, luego de agregar auxiliares apropiados si se desea, para obtener tabletas o núcleos de grageas. Excipientes adecuados son, en particular, rellenos como azúcares, incluidas lactosa, sacarosa, mannitol, o sorbitol; preparaciones de celulosa tales como, por ejemplo, almidón de maíz, almidón de trigo, almidón de arroz, almidón de papa, gelatina, goma tragacanto, metilcelulosa, hidroxipropilmetil-celulosa, carbometilcelulosa sódica; y/o polímeros fisiológicamente aceptables tales como polivinilpirrolidona (PVP). Si se desea, pueden agregarse agentes desagregantes, tales como polivinilpirrolidona entrecruzada, agar o ácido algínico o su sal tal como alginato de sodio.

[0051] Adicionalmente, una cubierta gastrorresistente puede ser útil, ya que puede ser deseable evitar la exposición de los compuestos de la invención al ambiente gástrico.

[0052] Composiciones farmacéuticas, que pueden usarse oralmente, incluyen cápsulas de dos piezas (***"push-fit capsules"***) hechas de gelatina así como cápsulas selladas, blandas, hechas de gelatina y un plastificante tal como glicerol o sorbitol. Las cápsulas duras pueden contener los ingredientes activos en mezcla con rellenos tales como lactosa, aglutinantes tales como almidones, lubricantes tales como talco o estearato de magnesio y, opcionalmente, estabilizantes.

[0053] En las cápsulas blandas, los compuestos activos pueden disolverse o suspenderse en líquidos apropiados, tales como aceites grasos, parafina líquida, o polietilén glicoles líquidos. Adicionalmente, pueden agregarse estabilizantes. Todas las formulaciones para administración oral deben estar en dosificaciones apropiadas para la vía de administración elegida.

[0054] Para inyección, los compuestos de la invención pueden formularse en soluciones acuosas, preferiblemente en amortiguadores fisiológicamente compatibles tales como solución de Ringer o Hank o amortiguador salino fisiológico. Para administración transmucosa y transdérmica, en la composición pueden emplearse penetrantes apropiados a la barrera a permearse. Tales penetrantes, incluidos por ejemplo DMSO o polietilén glicol, son conocidos en el arte.

[0055] Para administración por inhalación, los compuestos para uso de acuerdo con la presente invención se administran convenientemente en la forma de presentación en atomizador de aerosol de un envase a presión o nebulizador con el uso de un propelente adecuado, por ejemplo,, diclorodifluorometano, triclorofluorometano, dicloro-tetrafluoroetano o dióxido de carbono. En el caso de un aerosol a presión, la unidad posológica puede determinarse proveyendo una válvula para dispensar una cantidad medida. Pueden formularse cápsulas y cartuchos, por ejemplo, de gelatina para uso en un inhalador o insuflador, que contengan una mezcla de polvo de un compuesto y una base de polvo apropiada tal como lactosa o almidón.

[0056] Composiciones farmacéuticas para administración parenteral incluyen soluciones acuosas de los ingredientes activos en forma soluble en agua. Adicionalmente, pueden prepararse suspensiones de los compuestos activos como suspensiones oleosas apropiadas para inyección. Disolventes o vehículos lipófilos adecuados incluyen aceites grasos tales como aceite de ajonjolí, o ésteres de ácidos grasos tales como oleato de etilo, triglicéridos o

liposomas. Suspensiones acuosas para inyección pueden contener sustancias que incrementen la viscosidad de la suspensión, tales como carboximetilcelulosa sódica, sorbitol o dextrina. Opcionalmente, la suspensión puede contener además estabilizantes o agentes adecuados, que aumenten la solubilidad de los compuestos, para permitir la preparación de soluciones altamente concentradas.

[0057] Los compuestos de la presente invención pueden formularse igualmente en composiciones rectales tales como supositorios o enemas de retención, usando, por ejemplo, bases para supositorio convencionales tales como manteca de cacao u otros glicéridos.

[0058] Dependiendo de la gravedad y grado de reacción de la enfermedad a tratarse, la dosificación puede ser una administración única de una composición de liberación lenta, durando de varios días a varias semanas el curso del tratamiento o hasta que se efectúe la curación o se logre la disminución del estado patológico. La cantidad de una composición a administrarse dependerá, naturalmente, de muchos factores incluidos el sujeto que se está tratando, la gravedad de la afección, la forma de administración, el juicio del médico que formula. Los compuestos de la invención pueden administrarse oralmente o mediante inyección en una dosis desde 0.001 a 2.500 mg/kg por día. El rango de dosis para humanos adultos es generalmente desde 0.005 mg a 10 g/día. Tabletas u otras formas de presentación provistas en unidades discretas pueden contener convenientemente una cantidad de compuesto de la invención que es efectiva en tal posología o como un múltiplo de la misma, por ejemplo, unidades que contienen 5 mg a 500 mg, usualmente alrededor de 10 mg a 200 mg. La cantidad precisa de compuesto administrado a un paciente será la responsabilidad del médico encargado. Sin embargo, la dosis empleada dependerá de un número de factores, incluidos la edad y sexo del paciente, el trastorno preciso que se está tratando, y su gravedad. Además, la vía de administración puede variar dependiendo de afección y su gravedad.

[0059] Tal como se emplea en esta solicitud, y como se entendería por la persona experta en el arte, la enumeración de "un compuesto" tiene como finalidad incluir sales, solvatos y complejos de inclusión en ese compuesto. El término "solvato" se refiere a un compuesto de Fórmula I ó II en estado sólido, en donde moléculas de un disolvente apropiado se incorporan en la estructura cristalina. Un disolvente apropiado para administración terapéutica es fisiológicamente tolerable en la posología administrada. Ejemplos de disolventes apropiados para administración terapéutica son etanol y agua. Cuando el disolvente es agua, el solvato se denomina hidrato. En general, los solvatos se forman disolviendo el compuesto en el disolvente apropiado y aislando el solvato mediante enfriamiento o usando un anti-disolvente. Típicamente el solvato se seca o se destila a temperatura fija (***"is azeotroped"***) bajo condiciones ambientales. Los complejos de inclusión se describen en Remington: The Science and Practice of Pharmacy 19th Ed. (1995) volumen 1, páginas 176-177,el cual se incorpora en esta solicitud por referencia. Los complejos de inclusión más comúnmente empleados son aquellos con ciclodextrinas, y todos los complejos de ciclodextrina, naturales y sintéticos, se incluyen específicamente en las reivindicaciones.

[0060] El término "sal farmacéuticamente aceptable" se refiere a sales preparadas de ácidos o bases no tóxicos, farmacéuticamente aceptables incluidos ácidos inorgánicos y bases y ácidos orgánicos y bases. Cuando los compuestos de la presente invención son básicos, pueden prepararse sales de ácidos no tóxicos, farmacéuticamente aceptables, incluidos ácidos orgánicos e inorgánicos. Sales apropiadas de adición de ácido, farmacéuticamente aceptables, para los compuestos de la presente invención incluyen ácido acético, bencenosulfónico (besilato), benzoico, naftalenosulfónico, cítrico, etenosulfónico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, maleico, málico, mandélico, metanosulfónico, múcico, nítrico, pamoico, pantoténico, fosfórico,

succínico, sulfúrico, tartárico, p-toluenosulfónico, y similares. Cuando los compuestos contienen una cadena lateral ácida, sales de adición de base farmacéuticamente aceptables para los compuestos de la presente invención incluyen sales metálicas preparadas de aluminio, calcio, litio, magnesio, potasio, sodio y zinc o sales orgánicas preparadas de lisina, N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumina (N-metilglucamina) y procaína.

[0061] El término "prevenir" tal como se emplea en esta solicitud se refiere a administrar un medicamento con antelación para precaver o reducir la violencia del ataque. La persona de habilidad ordinaria en el arte médico (al cual se dirigen las reivindicaciones del presente método) reconoce que el término "prevenir" no es un término absoluto. En el arte médico se entiende que se refiere a la administración profiláctica de un medicamento para disminuir sustancialmente la probabilidad o seriedad de una afección, y éste es el sentido contemplado en esta solicitud.

[0062] Debe entenderse que además de los ingredientes particularmente ya mencionados, las formulaciones de esta invención pueden incluir otros agentes convencionales en el arte con respecto al tipo de formulación en cuestión, por ejemplo aquellos apropiados para administración oral pueden incluir agentes saborizantes.

[0063] Las composiciones pueden presentarse en un envase o dispensador, que puede contener una o más formas farmacéuticas unitarias con el ingrediente activo. Ejemplos de un envase incluyen hoja metálica o plástica, tal como un empaque blíster y un nebulizador para inhalación. El envase o dispensador puede acompañarse por instrucciones para la administración. Las composiciones que contienen un compuesto de la presente invención formulado en una sustancia portadora farmacéutica compatible pueden ponerse también en un recipiente apropiado y etiquetarse para tratamiento de una enfermedad indicada.

Indicaciones

[0064] Los compuestos de la presente invención son útiles en inhibir la actividad de Jak3 o en inhibir la actividad mediada por Jak3 y son útiles como agentes inmunosupresores para trasplantes de órganos y tejidos, incluidos trasplante de médula espinal y riñón, y en el tratamiento de enfermedades autoinmunitarias e inflamatorias y de complicaciones originadas en ellas.

[0065] Puede tratarse el rechazo de trasplante de órganos hiper-agudo, agudo y crónico. El rechazo hiperagudo ocurre en minutos luego del trasplante. El rechazo agudo ocurre generalmente en un término de seis a doce meses del trasplante. Los rechazos hiper-agudo y agudo son típicamente reversibles donde se tratan con agentes inmunosupresores. El rechazo crónico, caracterizado por la pérdida gradual de la función del órgano, es una preocupación constante de los recipiendarios de trasplante porque puede ocurrir en cualquier momento luego del trasplante.

[0066] Existen alrededor de 75 trastornos autoinmunitarios diferentes conocidos que pueden clasificarse en dos tipos, órgano-específicos (dirigidos principalmente a un órgano) y no-órgano-específicos (que afectan múltiples órganos).

[0067] Ejemplos de de trastornos autoinmunitarios órgano-específicos son diabetes insulino-dependientes (tipo I) que afecta el páncreas, la tiroiditis de Hashimoto y la enfermedad de Graves que afectan la glándula tiroides, la anemia perniciosa que afecta el estómago, la enfermedad de Cushing y la enfermedad de Addison que afectan las glándulas suprarrenales, hepatitis activa crónica que afecta el hígado; síndrome de ovario poliquístico (PCOS), enfermedad celíaca, psoriasis, síndrome de intestino irritable (IBD) y espondilitis anquilosante.

[0068] Ejemplos de trastornos autoinmunitarios no-órgano-específicos son artritis reumatoide, esclerosis múltiple, lupus sistémico y miastenia grave.

[0069] La diabetes tipo I resulta de la agresión selectiva de linfocitos T autorreactivos contra células β secretoras de insulina de los islotes de de Langerhans. La focalización en Jak3 en esta enfermedad se basa en la observación de que múltiples citocinas que señalan mediante la ruta Jak son conocidas por participar en la destrucción autoinmunitaria, mediada por los linfocitos T, de células β. De hecho, un inhibidor de Jak3, JANEX-1 demostró que prevenía el desarrollo de la diabetes autoinmunitaria espontánea en el modelo de ratones NOD de diabetes tipo I.

[0070] La enfermedad del injerto contra el anfitrión (GVHD) es un estado patológico iniciado por linfocitos T del donante que sigue con frecuencia al trasplante de médula espinal alógena (BMT). Una investigación experimental y clínica sustancial ha demostrado que los linfocitos T del donante son los principales mediadores y efectores de GVHD. Jak3 juega un papel clave en la inducción de GVHD, y el tratamiento con un inhibidor de Jak3, JANEX-1, demostró que atenúa la gravedad de GVHD (reseñado en Cetkovic-Cvrlje y Ucken, 2004).

[0071] Los mastocitos expresan Jak3, y Jak3 es un regulador clave de las respuestas de los mastocitos mediadas por IgE incluida la liberación de mediadores inflamatorios. Se demostró que Jak3 es un objetivo válido en el tratamiento de la reacción alérgica mediada por mastocitos.

[0072] Trastornos alérgicos asociados con la activación por mastocitos incluyen reacciones de hipersensibilidad inmediata tipo I tales como rinitis alérgica (fiebre del heno), urticaria alérgica (hives), angioedema, asma alérgica y anafilaxis, es decir, "choque anafiláctico." Estos trastornos se tratan o previenen por la inhibición de la actividad de Jak3, por ejemplo,

mediante la administración de un inhibidor de Jak3 de acuerdo con la presente invención.

[0073] De acuerdo con la presente invención, los inhibidores de Jak3 pueden administrarse profilácticamente, es decir, antes de la iniciación de la reacción alérgica aguda, o pueden administrarse luego de la iniciación de la reacción, o en los dos momentos.

[0074] La inflamación de tejidos y órganos ocurre en una amplia gama de trastornos y enfermedades y, en ciertas variaciones, resulta de la activación de la familia citocina de receptores. Trastornos inflamatorios ejemplares asociados con la activación de Jak3 incluyen, en una manera no limitante, inflamación de la piel debida a la exposición a radiación, asma, inflamación alérgica e inflamación crónica tal como queratoconjuntivitis seca.

[0075] Los compuestos de la presente invención son también útiles en tratar ciertas neoplasias malignas, incluidos cáncer de piel y neoplasia maligna hematológica tales como linfomas y leucemias. Un ejemplo de linfoma es linfoma anaplásico de células grandes (ALCL). La utilidad de los inhibidores de Jak3 de la presente invención para tratar ALCL se ha demostrado por los estudios presentados por Lai, R. *et al.* La activación de Jak3 se asocia significativamente con la expresión de ALK en linfoma anaplásico de células grandes. *Human Pathology* (2005) **36**, 939-944 and Harrington *et al.* VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. *Nature Medicine* (2004) 3, 262-267, los cuales se incorporan ambos en su totalidad en esta solicitud por referencia.

[0076] Un ejemplo de la leucemia es leucemia mielógena crónica CML). La utilidad de los inhibidores de Jak3 de la presente invención para tratar CML se ha demostrado por los estudios presentados por Harrington *et al.*, referenciados anteriormente. El estudio ya mencionado ha demostrado

además el tratamiento de leucemia mielógena aguda (AML) mediante experimentos *in vivo*.

[0077] Los compuestos de la presente invención son igualmente útiles en tratar neoplasias malignas no-hematológicas, incluidos cáncer de páncreas y colon. [Véase Harrington *et al., op. cit.* para pruebas *in vivo*.]

[0078] Los inhibidores de Jak3 de la presente invención son adicionalmente útiles en tratar la enfermedad cardiovascular.

[0079] Los siguientes ejemplos describirán la invención con más detalle, y se usan para los propósitos de ilustración únicamente, y no deben considerarse como limitantes de la invención que se está divulgando.

EJEMPLOS

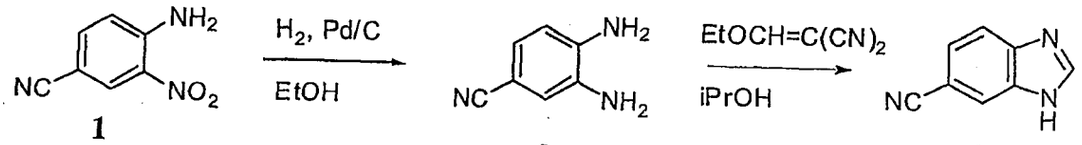
[0080] Las siguientes abreviaturas y términos tienen el significado indicado de principio a fin de la especificación:

Ac =	acetilo
Bu =	butilo
DCM =	diclorometano = cloruro de metileno = CH_2Cl_2
DEAD =	dietil azodicarboxilato
DIC =	diisopropilcarbodiimida
DIEA =	N,N-diisopropiletil amina
DMF =	N,N-dimetilformamida
DMSO =	sulfóxido de dimetilo
EA (EtOAc)=	acetato de etilo
GC =	cromatografía de gas
h =	horas
HOAc =	ácido acético
HOBt =	hidroxibenzotriazol
Me =	metilo

$Pd(dppf)2Cl_2$ =	dicloro[1,1'-bis(difenilfosfinoferroceno]paladio
Ph =	fenilo
PhOH =	fenol
RT =	temperatura de la sala
sat'd =	saturado
s- =	secundario
t- =	terciario
TBDMS =	t-butildimetilsililo
TFA =	ácido trifluoroacético
THF =	tetrahidrofurano
TMOF =	trimetil ortoformiato
TMS =	trimetilsililo
tosyl =	p-toluenosulfonilo
Trt =	trifenilmetilo

Ejemplos 1-15 describen la síntesis de ciertos precursores e intermedios de la invención.

[0081] Ejemplo 1. Síntesis de 3,4-Diaminobenzonitrilo



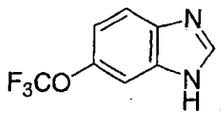
1 2 3

[0082] Una solución de 4-amino-3-nitrobenzonitrilo (1) (3.0 g) en etanol (80 mL) se roció durante 5 minutos con nitrógeno. Se agregó paladio sobre carbono (10%, 300 mg) y la mezcla se saturó con hidrógeno. La mezcla se agitó bajo un balón de hidrógeno durante 7 horas. La mezcla se roció con nitrógeno y se filtró a través de celita. El filtrado se concentró *in vacuo* para proporcionar el compuesto del título, 3,4- diaminobenzonitrilo (2).

[0083] Ejemplo 2: Síntesis de 3H-Benzo[d]imidazol-5-carbonitrilo

[0084] Una mezcla de 3,4-diaminobenzonitrilo (2) (1.0 g) y (etoximetilen) malononitrilo (1.4 g) se hizo refluir en 50 mL de alcohol isopropílico durante 16 horas. La mezcla se concentró *in vacuo* para proporcionar el compuesto del título, 3H-benzo[d]imidazol-5-carbo nitrilo (3).

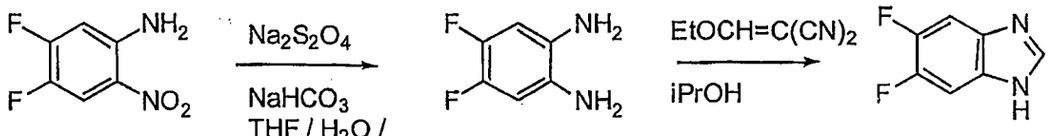
[0085] Ejemplo 3: Síntesis de 6-(Trifluorometoxi)-1H-benzo[d]imidazol



4

[0086] 6-(Trifluorometoxi)-1H-benzo[d]imidazol (**4**) se preparó en dos pasos de 2-nitro-4-(trifluorometoxi)anilina (**5**) usando procedimientos idénticos a los utilizados para preparar 3H-benzo[d]imidazol-5-carbonitrilo (**3**) de 4-amino-3-nitrobenzonitrilo (**1**, Ejemplos 1, 2).

[0087] Ejemplo 4: Síntesis de 5,6-Difluoro-1H-benzo[d]imidazol

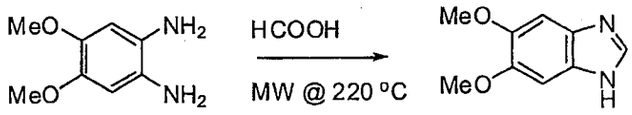


6 7 8

[0088] Una solución de 4,5-difluoro-2-nitroanilina (6)(1.0 g) en 30 mL de THF se trató con una solución compuesta de 6 g de $Na_2S_2O_4$ y 3 g $NaHCO_3$ en 30 mL de agua. Se agregó metanol (10 mL) luego de la adición de la solución acuosa de modo que la mezcla permaneciera homogénea. La mezcla se agitó durante dos horas y luego se diluyó con 100 mL de acetato de etilo y 100 mL de agua. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con 100 mL de cloruro de metileno. Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron para proporcionar el intermedio crudo 4,5-difluorobenceno-1,2-diamina (7). El intermedio se hizo refluir con (etoximetilen)malononitrilo (1.1 g) en 25 mL de alcohol isopropílico durante 16 horas. La mezcla se concentró *in vacuo* y el producto crudo resultante se suspendió en agua y se filtró. El precipitado se lavó con agua

y se secó con aire para proporcionar 380 mg de 5,6-difluoro-1H-benzo[d]imidazol (**8**).

[0089] Ejemplo 5: Síntesis de 5,6-Dimetoxi-1H-benzo[d]imidazol

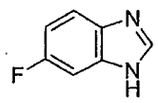


9 **10**

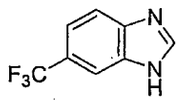
[0090] El compuesto del título 5,6-dimetoxi-1H-benzo[d]imidazol (**10**) se preparó calentando diclorhidrato de 4,5-dimetoxi-1,2-fenilendiamina (**9**) en ácido fórmico a 220 °C en un microondas seguida por concentración *in vacuo*.

[0091] Ejemplo 6: Síntesis de 6-Fluoro-1H-benzo[d]imidazol (**11**) y 6-(trifluorometil)-1H-benzo[d]imidazol (**12**).

[0092] Los compuestos del título se prepararon como se describe en la Publicación de Solicitud de los Estados Unidos No. 2004/0087601, de algunos de los presentes inventores.



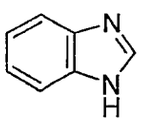
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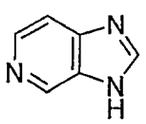
12

[0093] Ejemplo 7: Benzimidazol (**13**), 5-azabenzimidazol (**14**), 6-cloro-5-fluorobenzimidazol (**15**), y 5-metilbenzimidazol (**16**).

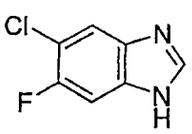
[0094] Los compuestos del título se obtuvieron en el comercio.



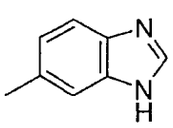
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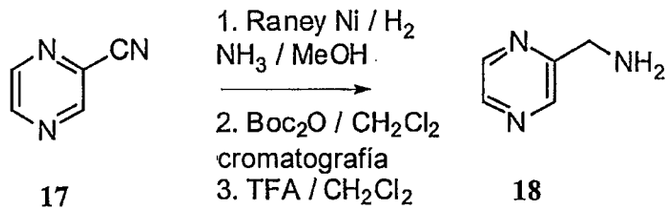


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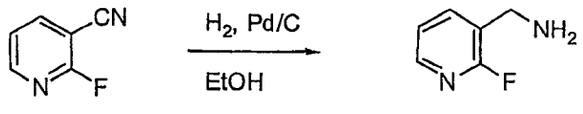
[0095] Ejemplo 8. Síntesis de la amina primaria, pirazin-2-ilmetanamina



17 18

[0096] Catalizador níquel de Raney se lavó cuidadosamente con THF y metanol asegurándose de que el catalizador permaneciera húmedo. El peso del catalizador húmedo fue de 2.5 g luego del lavado. Este material se agregó a una solución de pirazincarbonitrilo (**17**) (3.0 g) en 7N de amoníaco metanólico (120 mL). La mezcla se agitó bajo una atmósfera de 50 p.s.i. de hidrógeno durante 1.5 horas. La mezcla se filtró y el filtrado se concentró *in vacuo* para proporcionar el compuesto crudo del título. La purificación se llevó a cabo mediante conversión de la mina cruda en el *terc*-butil carbamato con exceso de di-*terc*-butil dicarbonato en cloruro de metileno. Cromatografía en columna (70:27:3 hexanos:acetato de etilo:metanol) proporcionó 0.50 g de *terc*-butil pirazin-2-ilmetilcarbamato puro. Se obtuvo pirazin-2-ilmetanamina pura (**18**) como la sal TFA de la desprotección del carbamato con 1:1 TFA / CH_2Cl_2.

[0097] Ejemplo 9: Síntesis de 3-Aminometil-2-fluoropiridina



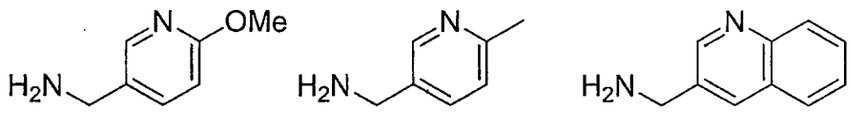
19 20

[0098] Un matraz de fondo redondo se cargó con 0.3g (2.46mM) de 3-ciano-2-fluoropiridina (19), la cual se diluyó luego en 20mL EtOH. La solución se enjuagó con argón, y luego, estando bajo una cubierta de argón, se agregaron 60mg de 10% Pd/C (20% en peso). En seguida, el sistema se selló mediante un tabique y se puso bajo vacío. Se agregó entonces un balón de hidrógeno, y la reacción se agitó durante tres horas (seguida por TLC). La reacción se puso nuevamente bajo vacío, luego se expuso al aire, y se filtró (manteniendo húmedo el catalizador). La solución resultante se

secó y se evaporó para producir 0.28g (90%) del compuesto del título, 3-aminometil-2-fluoropiridina (20).

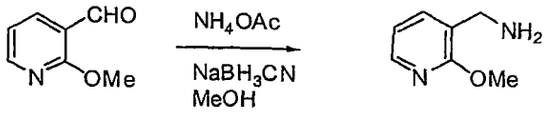
[0099] Ejemplo 10: Síntesis de 3-Aminometil-6-metoxipiridina (21), 3-Aminometil-6-metilpiridina (22), y 3-Aminometilquinolina (23).

[00100] Las aminas del título se obtuvieron de los nitrilos correspondientes utilizando el mismo procedimiento que el empleado para obtener 3-aminometil-2-fluoropiridina (**20**) de 3-ciano-2-fluoropiridina (véase Ejemplo 9).



21 **22** **23**

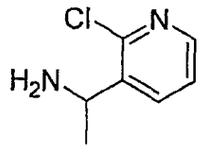
[00101] Ejemplo 11: Síntesis de 3-Aminometil-2-metoxipiridina



24 **25**

[00102] Un matraz de fondo redondo se cargó con 0.44g (3.23mM) de 2-metoxi-3-piridina carboxaldehído (24), 1.24g (16.15mM) de acetato de amonio, y 0.61g (19.69mM) de cianoborohidruro de sodio. El matráz se enjuagó entonces con argón, y luego se agregaron 50mL de MeOH seco mediante una jeringa. La reacción se agitó durante 2 días, punto en el cual el MeOH se evaporó en su totalidad. Se agregaron 25mL de agua, y la mezcla se llevó a pH 2 con HCl concentrado. Esto se extrajo dos veces con EtOAc para retirar el subproducto alcohol. La mezcla se llevó a pH 10 usando miniesferas de hidróxido de sodio, se saturó con NaCl, y se extrajo dos veces con DCM y una vez con EtOAc. Los orgánicos combinados se secaron y se evaporaron para producir 0.31g (69%) de 3-aminometil-2-metoxipiridina (25).

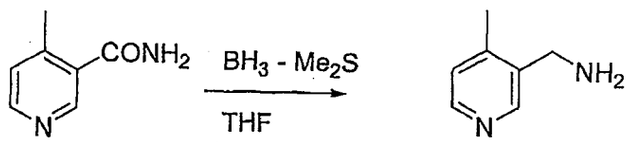
[00103] Ejemplo 12: Síntesis de 3-(α-aminoetil)-2-cloropiridina (**26**)



26

[00104] La amina del título se obtuvo de la cetona correspondiente usando el mismo procedimiento que se utilizó para obtener 3-aminometil-2-metoxipiridina de 2-metoxi-3-piridina carboxaldehído (**24**; Ejemplo 11).

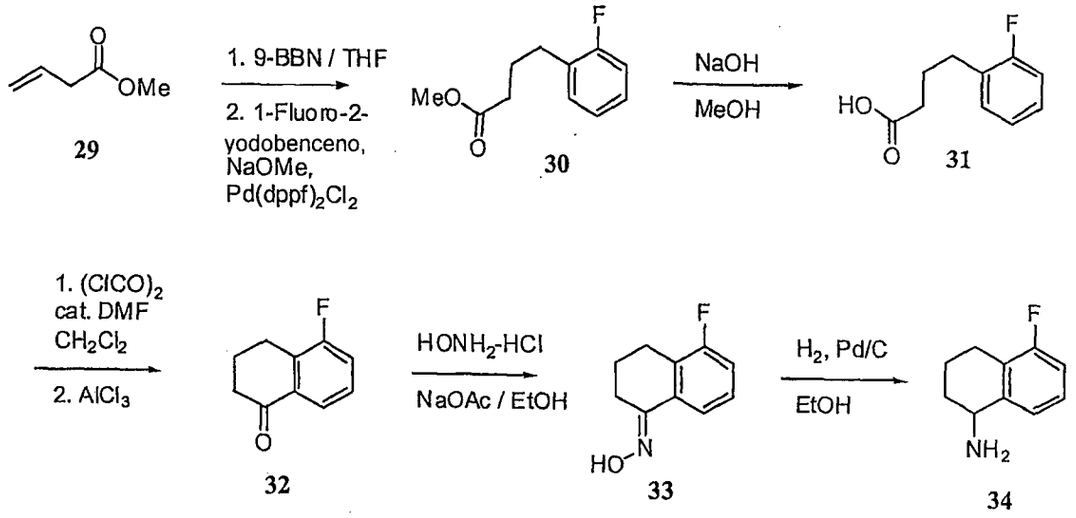
[00105] Ejemplo 13: Síntesis de 3-aminometil-4-metilpiridina



27 **28**

[00106] Un matraz de fondo redondo se cargó con 0.45g (3.30mM) de 4-metilnicotinamida (**27**). El matraz se enjuagó con argón, y se agregaron 50mL de THF seco mediante jeringa. La solución resultante se enfrió a 0° C, y se agregaron 2.5mL (4.96mM) de una solución 2M de complejo borano-sulfuro de dimetilo (en THF). Se conectó una fuente de burbujas, y la solución se calentó a temperatura de la sala de un día para otro. La solución se extinguió con MeOH, y se secó y se evaporó para producir 0.38g (95%) de 3-aminometil-4-metilpiridina (28).

[00107] Ejemplo 14: Síntesis de 5-fluoro-1,2,3,4-tetrahidronaftalen-1-amin



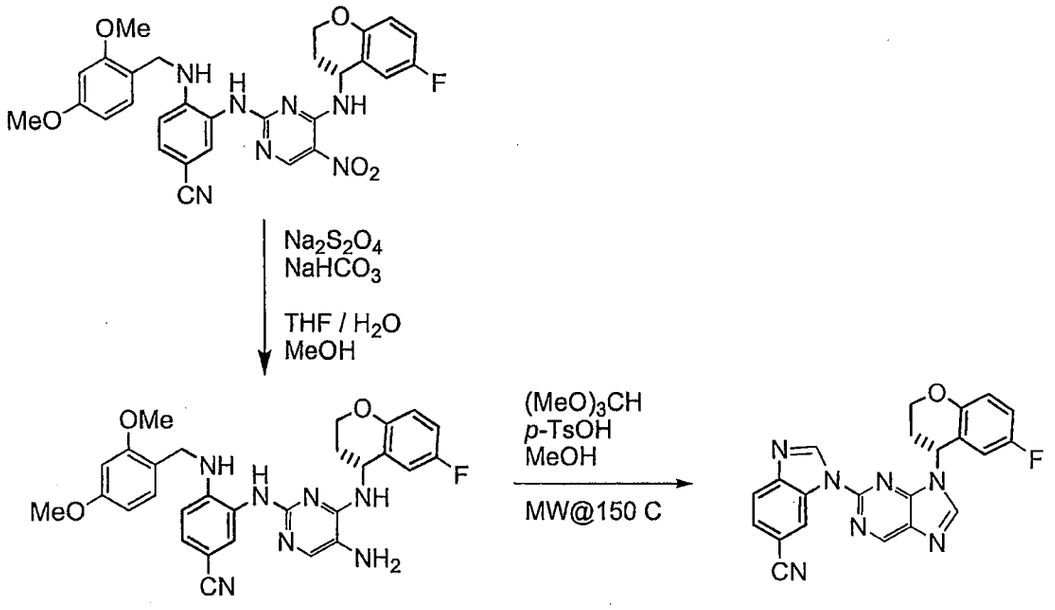
[00108] Metil 4-(2-fluorofenil)butanoato (2-(4-metilbutanoato) fluorobenceno, **30**). Un matraz de fondo redondo se selló con un tabique de caucho, se enjuagó con argón, luego se cargó con 5.32mL de metil 3-butenoato (**29**) y 100mL de una solución 0.5M de 9-BBN en THF. La solución se agitó a temperatura de la sala durante tres horas. Un matraz de fondo redondo de 2 cuellos se equipó con un condensador y se enjuagó con argón, luego se cargó con 7.36g de metóxido de sodio y 1.11g de $Pd(dppf)_2Cl_2$. A esta mezcla se agregaron 20mL de THF seco y 5.22mL de 1-fluoro-2-yodobenceno. La solución de hidroboración se agregó mediante cánula y la mezcla resultante se hizo refluir durante 16 horas. La solución se enfrió a temperatura de la sala, se diluyó con 150mL de agua, y se extrajo tres veces con éter. Las capas orgánicas combinadas se lavaron con salmuera, se secaron, y se evaporaron. Cromatografía en columna (5% EtOAc/hexanos) produjo 1.79 g metil 4-(2-fluorofenil)butanoato (**30**).

[00109] Ácido 4-(2-fluorofenil)butanoico (31). Un matraz de fondo redondo se cargó con 1.79g de 2-(4-metilbutanoato)fluorobenceno, lo cual se disolvió en 17mL de MeOH. A esta solución se agregó una solución de 1 g de hidróxido de sodio. La mezcla resultante se agitó 20 horas a temperatura de la sala. El disolvente se evaporó y el material crudo se diluyó con 15mL de 0.5M HCl. La extracción con DCM tres veces produjo 1.17g (92%) de ácido 4-(2- fluorofenil)butanoico (31).

[00110] 5-Fluoro-3,4-dihidronaftalen-1(2H)-ona (32). Un matraz de fondo redondo se cargó con 0.15 g de ácido 4-(2-fluorofenil)butanoico, el cual se disolvió en 20mL DCM y se enfrió a 0 °C. Se agregó cloruro de oxalilo (0.15mL), seguido por 1 gota de DMF. Se conectó un tubo secador, y la solución se agitó a 0 °C durante 2 horas. Se agregó cloruro de aluminio (0.121g) y la solución se dejó calentar lentamente a temperatura de la sala de un día para otro. La mezcla se vertió sobre agua helada, y se extrajo tres veces con DCM. Las capas orgánicas combinadas se lavaron con 0.5 MNaOH y salmuera. La fase orgánica se secó, se evaporó y se purificó por cromatografía en columna (eluyendo con 20% EtOAc/Hexanos), para producir 0.07g (53%) de 5-fluoro-3,4-dihidronaftalen-1(2H)-ona (32).

[00111] 5-Fluoro-1,2,3,4-tetrahidronaftalen-1-amina (34). Un matraz de fondo redondo se cargó con 0.5g de 5-fluoro-3,4-dihidronaftalen-1(2H)-ona, 0.28g de clorhidrato de hidroxilamina, y 0.34g de acetato de sodio. Se conectó un condensador, y el matraz se purgó con argón. Se agregaron 20mL de EtOH seco, y la mezcla se agitó a reflujo durante 18 horas. La solución se enfrió a temperatura de la sala, se diluyó con EtOAc, y se lavó con agua. La fase orgánica se secó con sulfato de sodio y se evaporó para producir 0.5g del intermedio 5-fluoro-3,4-dihidronaftalen-1(2H)-ona oxima (**33**), el cual se redujo con Pd/C en EtOH con hidrógeno (50psi), para producir 0.43g (86%) de 5-fluoro-1,2,3,4-tetrahidronaftalen-1-amina (**34**).

[00112] Ejemplo 15: Síntesis de 3-(9-((*R*)-6-fluorocroman-4-il)-9*H*-purin-2-il)-3*H*-benzo[*d*]imidazol-5-carbonitrilo

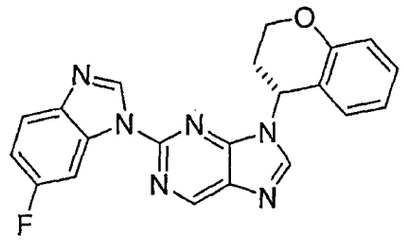


[00113] A una solución de (*R*)-4-(2,4-dimetoxibencilamino)-3-(4-(6-fluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino)benzonitrilo (preparado como se describe más adelante en Ejemplo 26, parágrafo [**0157**]) (12 mg) en THF (5 mL) se agregó una solución premezclada de hidrosulfito de sodio (100 mg) y bicarbonato de sodio (50 mg) en agua (10 mL). Se agregó asimismo MeOH (1 mL) para ayudar a la solución de la mezcla, la cual se agitó a temperatura de la sala durante 30 minutos, cuando se agregó cloruro de sodio para saturar la solución. La mezcla resultante se extrajo con EtOAc (2x), los orgánicos combinados se secaron, se filtraron y se evaporaron para proporcionar (*R*)-4-(2,4-dimetoxibencilamino)-3-(5-amino-4-(6-fluorocroman-4-ilamino)pirimidin-2-ilamino)benzonitrilo que se utilizó tal como estaba para el siguiente paso, $MH^+ = 542$.

[00114] A un vial de microondas se agregó la amina anterior, una cantidad catalítica de monohidrato de ácido *para*-toluenosulfónico, ortoformiato de trimetilo (0.5 mL) y MeOH (1 mL). El vial se tapó y se calentó en un horno Emrys Optimizer a 150 °C durante 5 minutos. La mezcla se concentró *in vacuo*, y se purificó por RP HPLC para proporcionar 4.6 mg del producto del título como la sal TFA, NMR $CDCl_3$ ^1H δ 9.5 (br s, 1H), 9.3 (s, 1H), 9.0 (s, 1H), 8.2 (br s, 1H), 8.0 (d, 1H), 7.7 (d, 1H), 7.1-7.0 (m, 2H), 6.6 (dd,

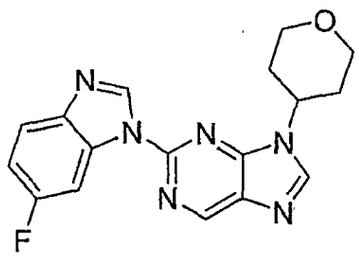
1H), 6.0 (t, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 2.7 (m, 2H); ^{19}F δ -121, -76 ppm; $MH^+ = 412$.

[00115] Síntesis de 9-((*R*)-Croman-4-il)-2-(6-fluoro-1*H*-benzo[*d*] imidazol-1-il)-9*H*-purina.



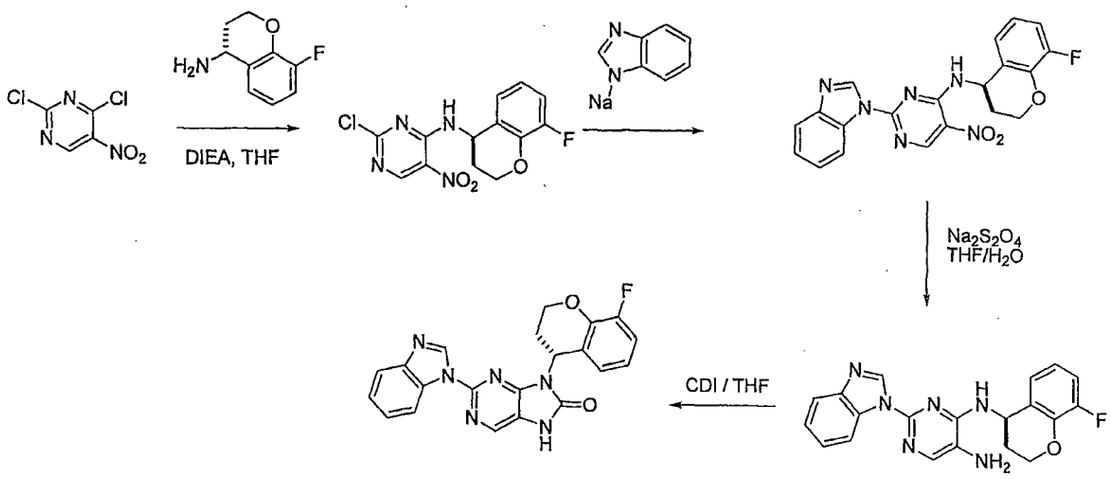
[00116] El compuesto del título como sal de TFA se sintetizó de (*R*)-*terc*-butil2-(4-(croman-4-ilamino)-5-nitropirimidin-2-ilamino)-4-fluorofenilcarbamato mediante el procedimiento descrito en Ejemplo 15. ^1H NMR (300 MHZ, $CDCl_3$): δ 9.15 (s, 2H), 8.27 (dd, 1H), 7.89 (s, 1H), 7.78 (dd, 1H), 7.32 (td, 1H), 7.32 (td, 1H), 7.13 (td, 1H), 7.1-6.9 (m, 3H), 6.00 (t, 1H), 4.4-4.3 (m, 2H), 4.2-4.1 (m, 2H), 2.7-2.5 (m, 2H). ^{19}F NMR: δ - 116.4.

[00117] Síntesis de 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-(tetrahidro-2*H*-piran-4-il)-9*H*-purina.



[00118] El compuesto del título como sal de TFA se sintetizó de *terc*-butil 4-fluoro-2-(5-nitro-4-(tetrahidro-2H-piran-4-ilamino)pirimidin-2-ilamino) fenilcarbamato mediante el procedimiento descrito en Ejemplo 15. ^1H NMR (300 MHz, $CDCl_3$): δ 9.73 (s, 1H), 9.29 (s, 1H), 8.5-8.6 (m, 1H), 8.40 (s, 1H), 7.9-8.1 (m, 1H), 7.3-7.4 (m, 1H), 4.8-5.0 (m, 1H), 4.2-4.4 (m, 2H), 3.7-3.8 (m, 2H), 3.05 (d, 1H), 2.2-2.4 (m, 3H). ^{19}F NMR: δ -112.4.

[00119] Ejemplo 16: Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona



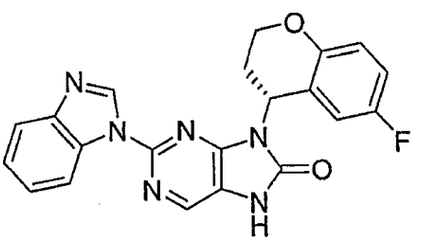
[00120] **2-(1*H*-Benzo[d]imidazol-1-il)-N-((*R*)-8-fluorocroman-4-il)-5-nitropirimidin-4-amina**. (*R*)-8-Fluorocroman-4-amina (60 mg, Ejemplo 29) se agregó a una solución de 2,4-dicloro-5-nitropirimidina (70 mg) y DIEA (0.14 mL) en THF (5 mL) a -78 °C. La mezcla de reacción se agitó durante 15 minutos más a -78 °C, luego se retiró del baño frío y se dejó calentar a temperatura de la sala. Una solución molar de la sal de sodio de benzimidazol (0.7 ml, solución patrón concentrada preparada mediante la adición de hidruro de sodio a una solución de benzimidazol en THF) se agregó al intermedio de reacción ((*R*)-2-cloro-*N*-(8-fluorocroman-4-il)-5-nitropirimidin-4-amina) y la mezcla resultante se agitó a temperatura de la sala de un día para otro. La purificación mediante cromatografía en columna (elución con 1 MeOH/DCM) produjo el compuesto del título (120 mg), $MH^+ = 407$.

[00121] **2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona**. Una solución recién preparada de hidrosulfito de sodio (téc., 0.5 g) y bicarbonato de sodio (0.25 g) en H_2O (5 mL) se agregó a una solución del anterior compuesto nitro (120 mg) en THF (10 mL). La mezcla se agitó vigorosamente durante 30 minutos, luego se extrajo con EtOAc (2 x) y DCM (2 x), los orgánicos combinados se lavaron con salmuera, se secaron, se filtraron y se concentraron para producir el

intermedio 2-(1*H*-benzo[*d*]imidazol-1-il)-N^4-((*R*)-8-fluorocroman-4-il)pirimidin-4,5-diamina que se utilizó tal como estaba en el siguiente paso.

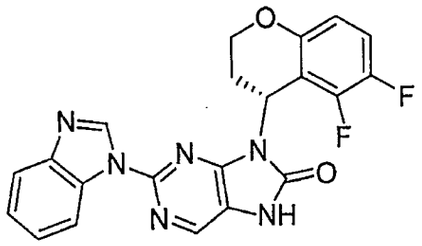
[00122] Carbonildiimidazol (0.2 g) se agregó a una solución de la amina anterior en THF (10 mL). La mezcla resultante se agitó a temperatura de la sala de un día para otro, se agregó gel de sílice, luego se retiraron los disolventes bajo presión reducida y se purificó mediante cromatografía en columna, elución con 5 % MeOH/DCM, para proporcionar el compuesto del título (28 mg), MH^+ = 403, ^{1}H NMR ($CDCl_3$) δ 10.6 (s, 1H), 8.9 (s, 1H), 8.3 (s, 1H), 7.8 (m, 2H), 7.3 (m, 2H), 7.0 (m, 1H), 6.7 (m, 1H), 5.9 (dd, 1H), 4.7 (m, 1H), 4.4 (t, 1H), 2.7 (m, 1H), 2.3 (m, 1H) ppm, ^{19}F NMR δ -135.7 (m). HPLC quiral - sin evidencia de otro enantiómero, Método; Chiralcel OD-H (columna analítica 0.46 x 25 cm, Daicel Chemical Industries) isocrática 15 % (0.05% TFA/EtOH) 85 % (0.05 % TFA/Hex), Rt = 19.5 minutos (*R*)-enantiómero, Rt = 22.4 minutos (*R*)-enantiómero.

[00123] Síntesis de 2-(1H-benzo[d]imidazol-1-il)-9-((R)-6-fluorocroman-4-il)-7H-purin-8(9H)-ona.



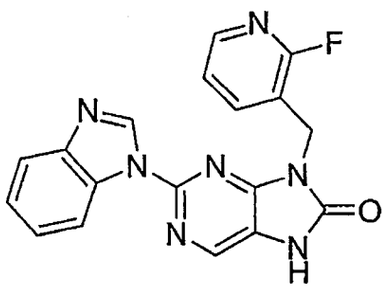
[00124] El compuesto del título se sintetizó de (R)-6-fluorocroman-4-amina utilizando los procedimientos descritos en Ejemplo 16. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.28 (s, 1H), 8.82 (s, 1H), 8.28 (s, 1H), 7.94 (d, 1H), 7.79 (d, 1H), 7.2-7.4 (m, 2H), 6.8-7.1 (m, 2H), 6.66 (dd, 1H), 5.92 (br t, 1H), 4.55 (m, 1H), 4.33 (m, 1H), 2.90 (m, 1H), 2.31 (m, 1H).

[00125] Síntesis de 2-(1H-benzo[d]imidazol-1-il)-9-((R)-5,6-difluorocroman-4-il)-7H-purin-8(9H)-ona.



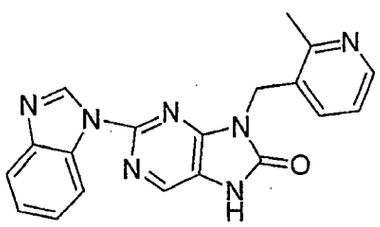
[00126] El compuesto del título se sintetizó de (R)-5,6-difluorocroman-4-amina (obtenida por resolución de (+/-)-5,6-difluorocroman-4-amina utilizando el procedimiento de resolución descrito en Ejemplo 29) utilizando los procedimientos descritos en Ejemplo 16. ^{1}H NMR (300 MHz, $CDC1_3$+5%CD_3OD): δ 8.62 (s, 1H), 8.18 (s, 1H), 8.0-8.1 (m, 1H), 7.6-7.7 (m, 1H), 7.2-7.3 (m, 1H), 6.9-7.1 (m, 2H), 6.7-6.8 (m, 1H), 5.86 (br t, 1H), 4.4-4.5 (m, 1H), 4.2-4.3 (m, 1H), 2.5-2.6 (m, 1H), 2.3-2.4 (m, 1H).

[00127] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((2-fluoropiridin-3-il)metil)-7H-purin-8(9*H*)-ona.



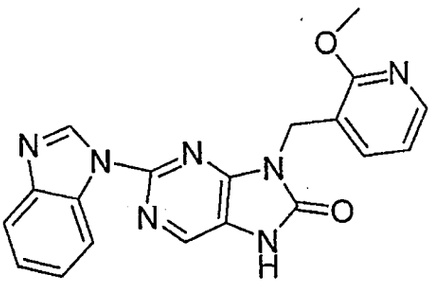
[00128] El compuesto del título se sintetizó de 3-aminometil-2-fluoropiridina mediante el procedimiento descrito en Ejemplo 16. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 9.0 (d, 1H), 8.4 (m, 1H), 8.2 (d, 1H), 7.8 (m, 2H), 7.4 (m, 3H), 7.2 (t, 1H), 4.3 (s, 2H), ppm.

[00129] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((2-metilpiridin-3-il)metil)-7*H*-purin-8(9*H*)-ona.



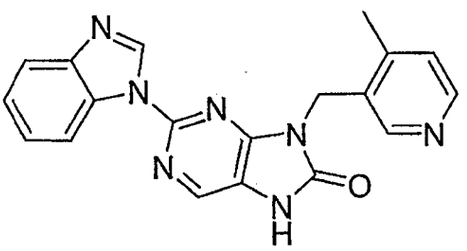
[00130] El compuesto del título se sintetizó de 3-aminometil-2-metilpiridina mediante el procedimiento descrito en Ejemplo 16. ^{1}H-NMR ($CDCl_3$) δ 9.4 (s, 1H), 8.6 (d, 1H), 8.5 (d, 1H), 8.4 (d, 1H), 8.2 (s, 1H), 7.7 (d, 1H), 7.6 (t, 1H), 7.4 (m, 2H), 5.2 (s, 2H), 2.9 (s, 3H), ppm.

[00131] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((2-metoxipiridin-3-il)metil)-7*H*-purin-8(9*H*)-ona.



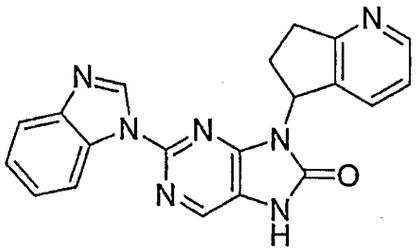
[00132] El compuesto del título se sintetizó de 3-aminometil-2-metoxipiridina mediante el procedimiento descrito en Ejemplo 16. ^{1}H-NMR ($CDCl_3$) δ 9.1 (s, 1H), 8.6 (d, 1H), 8.2 (s, 1H), 8.0 (d, 1H), 7.7 (s, 1H), 7.7 (d, 1H), 7.5 (d, 1H), 7.3 (m, 2H), 6.80 (t, 1H), 5.1 (s, 2H), 3.9 (s, 3H), ppm.

[00133] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((4-metilpiridin-3-il)metil)-7*H*-purin-8(9*H*)-ona.



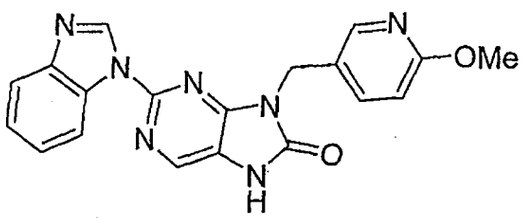
[00134] El compuesto del título se sintetizó de 3-aminometil-4-metilpiridina mediante el procedimiento descrito en Ejemplo 16. ^{1}H-NMR ($CDCl_3$) δ 8.9 (s, 1H), 8.5 (s, 1H), 8.3 (m, 1H), 8.2 (m, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.3 (m, 1H), 7.0 (m, 2H), 5.2 (s, 2H), 2.5 (s, 3H), ppm.

[00135] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(6,7-dihidro-5H-ciclopenta[*b*]piridin-5-il)-7*H*-purin-8(9*H*)-ona.



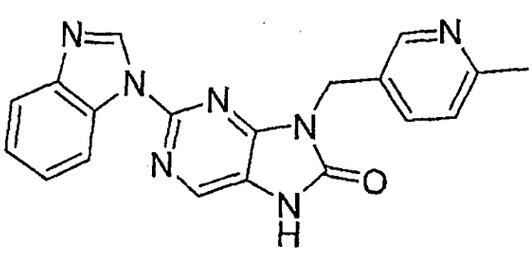
[00136] El compuesto del título se sintetizó de 6,7-dihidro-5*H*-ciclopenta[*b*]piridin-5-amina (WO 2003/045924) mediante el procedimiento descrito en Ejemplo 16. ^{1}H-NMR ($CDCl_3$) δ 8.8 (s, 1H), 8.6 (d, 1H), 8.3 (s, 1H), 7.8 (dd, 1H), 7.6 (dd, 1H), 7.4 (d, 1H), 7.3-7.1 (m, 3H), 6.3 (t, 1H), 3.6-3.5 (m, 1H), 3.4-3.2 (m, 1H), 2.9- 2.6 (m, 2H) ppm.

[00137] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((6-metoxipiridin-3-il)metil)-7*H*-purin-8(9*H*)-ona.



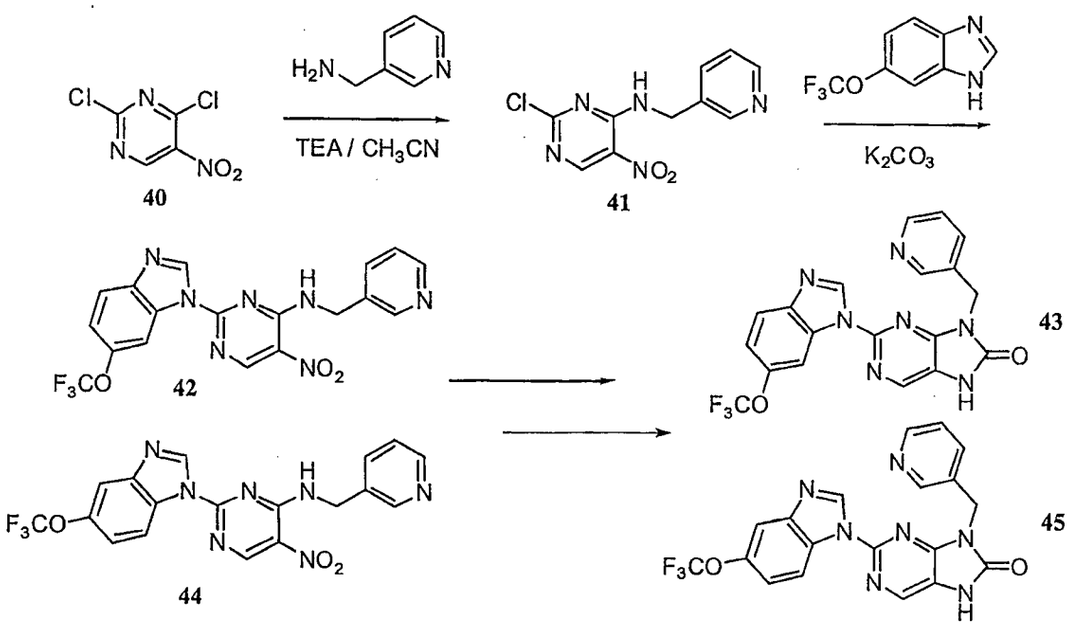
[00138] El compuesto del título se sintetizó de 3-aminometil-6-metoxipiridina mediante el procedimiento descrito en Ejemplo 16. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.5 (d, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.8 (m, 2H), 7.4 (t, 2H), 6.7 (d, 1H), 5.1 (s, 2H), 3.8 (s, 3H) ppm.

[00139] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-((6-metilpiridin-3-il)metil)-7*H*-purin-8(9*H*)-ona.



[00140] El compuesto del título se sintetizó de 3-aminometil-6-metilpiridina mediante el procedimiento descrito en Ejemplo 16. ^{1}H-NMR ($CDCl_3$) δ 9.5 (s, 1H), 9.2 (s, 1H), 8.9 (s, 1H), 8.7 (d, 1H), 8.4 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 7.5 (m, 2H), 5.5 (s, 2H), 2.6 (s, 3H) ppm.

[00141] Ejemplo 17: Síntesis no regioespecífica de derivados de benzimidazol purinona: Síntesis de 5-Nitro-N-(piridin-3-ilmetil)-2-(6-(trifluorometoxi)-1H-benzo[d]imidazol-1-il)pirimidin-4-amina (**42**) y 5-nitro-N-(piridin-3-ilmetil)-2-(5-(trifluorometoxi)-1H-benzo[d]imidazol-1-il)pirimidin-4-amina (**44**).



[00142] **2-Cloro-5-nitro-N-(piridin-3-ilmetil)pirimidin-4-amina (41).** Una solución de 2,4-dicloro-5-nitropirimidina (**40**) (5 g) en cloruro de metileno (60 mL) se enfrió a -78 °C y se trató con 3-(aminometil)piridina (2.8 g). La mezcla se agitó a -78 °C durante seis horas, y se concentró *in vacuo* a temperatura de la sala para proporcionar 2-cloro-5-nitro-N-(piridin-3-ilmetil)pirimidin-4-amina cruda (41), la cual se usó sin purificación posterior.

[00143] 5-Nitro-N-(piridin-3-ilmetil)-2-(6-(trifluorometoxi)-1H-benzo[d] imidazol-1-il)pirimidin-4-amina (**42**) y 5-nitro-N-(piridin-3-ilmetil)-2-(5-

(trifluorometoxi)-1*H*-benzo[*d*]imidazol-1-il)pirimidin-4-amina (**44**). Una suspensión de 2-cloro-5-nitro-N-(piridin-3-ilmetil)pirimidin-4-amina cruda (52 mg) en acetonitrilo (10 mL) se trató con 6-(trifluorometoxi)-1H-benzo[d]imidazol (40 mg), carbonato de potasio (0.5 g), y se calentó a 80 °C durante cuatro horas. La mezcla se diluyó con agua y se extrajo con cloruro de metileno. La capa orgánica se separó, se secó con sulfato de sodio, se filtró y se concentró *in vacuo*. Cromatografía en columna (70:22:8 cloruro de metileno: acetato de etilo metanol) proporcionó 12 mg de 5-nitro-N-(piridin-3-ilmetil)-2-(5- (trifluorometoxi)-1H-benzo[d]imidazol-1-il)pirimidin-4-amina como el primer isómero eluyente y 15 mg de 5-nitro-N-(piridin-3-ilmetil)-2-(6-(trifluorometoxi)-1H-benzo[d]imidazol-1-il) pirimidin-4-amina como el segundo isómero eluyente.

[00144] Isómero R_f alto: ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.9 (s, 1H), 8.8 (m, 1H), 8.6 (s, 1H), 8.5 (d, 1H), 8.2 (d, 1H, asignado: H-7 del anillo benzimidazol), 7.6 (d, 1H), 7.6 (s, 1H, asignado: H-4 del anillo benzimidazol), 7.2 (dd, 1H), 4.9 (d, 2H).

[00145] Isómero R_f bajo: ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.9 (s, 1H), 8.8 (m, 1H), 8.6 (s, 1H), 8.5 (d, 1H), 8.2 (s, 1H, asignado: H-7 del anillo benzimidazol), 7.7 (d, 1H, asignado: H-4 del anillo benzimidazol), 7.6 (d, 1H), 7.2 (dd, 1H), 7.1 (d, 1H), 4.9 (d, 2H).

[00146] Ejemplo 18: Síntesis no regioespecífica de derivados de benzimidazol purinona: Síntesis de 9-(Piridin-3-ilmetil)-2-(6-(trifluorometoxi)-1H-benzo[d]imidazol-1-il)-7H-purin-8(9H)-ona (43) y 9-(piridin-3-ilmetil)-2-(5-(trifluorometoxi)-1H-benzo[d]imidazol-1-il)-7*H*-purin-8(9*H*)-ona (45).

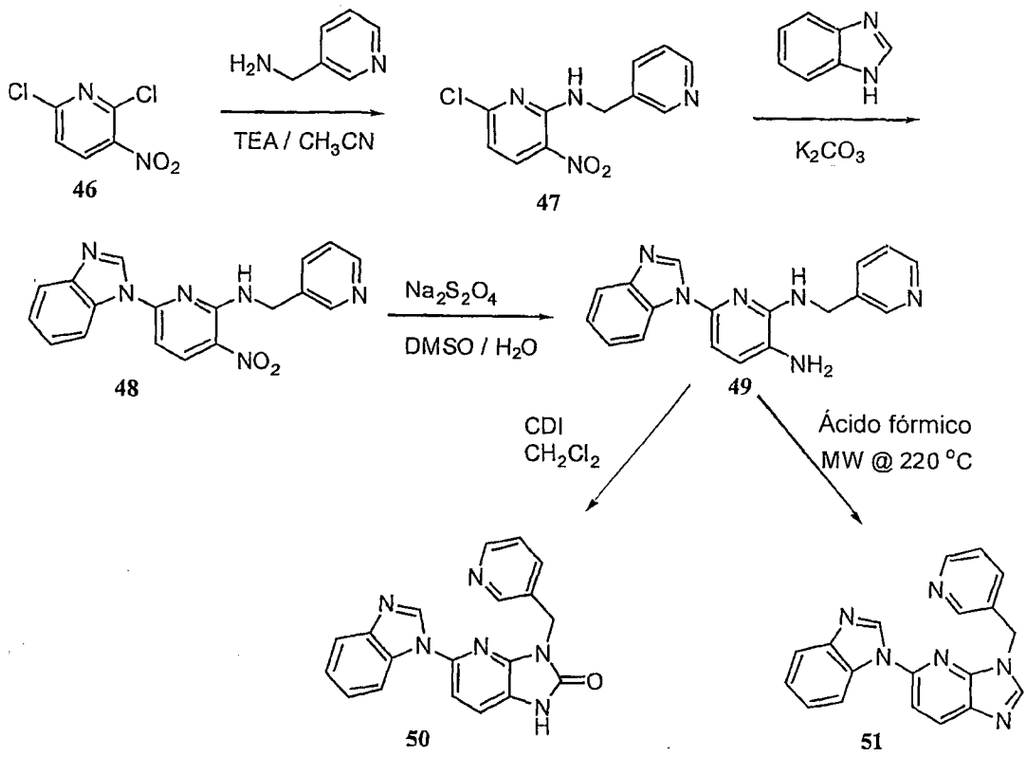
[00147] Los compuestos del título se sintetizaron de 5-nitro-N-(piridin-3-ilmetil)-2-(6-(trifluorometoxi)-1*H*-benzo[d]imidazol-1-il)pirimidin-4-amina (**42**) y 5-nitro-N-(piridin-3-ilmetil)-2-(5-(trifluorometoxi)-1H-benzo[d]

imidazol-1-il)pirimidin-4-amina (**44**) utilizando los mismos procedimientos que se emplearon para convertir (R)-*terc*-butil 2,4-dimetoxibencil(5-nitro-6-(1-(piridin-3-il)etilamino)piridin-2-il)carbamato en (R)-*terc*-butil 2,4-dimetoxibencil(2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidro-1H-imidazo [4,5-b]piridin-5-il)carbamato (67; Ejemplo 22 más adelante).

[00148] Isómero 6-trifluorometoxi (no sal): ^{1}H-NMR (CD_3OD) δ 9.3 (s, 1H), 8.8 (br s, 1H), 8.6 (s, 1H, asignado: H-7 del anillo benzimidazol), 8.6 (m, 1H), 8.4 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H, asignado: H-4 del anillo benzimidazol), 7.5 (dd, 1H), 7.4 (dd, 1H), 5.4 (s, 2H).

[00149] Isómero 5-trifluorometoxi (no sal): ^{1}H-NMR (CD_3OD) δ 9.3 (s, 1H), 8.8 (s, 1H), 8.7 (d, 1H, asignado: H-7 del anillo benzimidazol), 8.5 (d, 1H), 8.3 (s, 1H), 7.9 (d, 1H), 7.6 (s, 1H, asignado: H-4 del anillo benzimidazol), 7.4 (dd, 1H), 7.3 (dd, 1H), 5.3 (s, 2H).

[00150] Ejemplo 19: Síntesis no regioespecífica de una un derivado de oxoimidazopiridina e imidazopiridina: Síntesis de 5-(1*H*-Benzo[d]imidazol-1-il)-3-(piridin-3-ilmetil)-1H-imidazo[4,5-b]piridin-2(3H)-ona (**50**) y 5-(1*H*-benzo[d]imidazol-1-il)3-(piridin-3-ilmetil)-3H-imidazo[4,5-b]piridina (**51**).



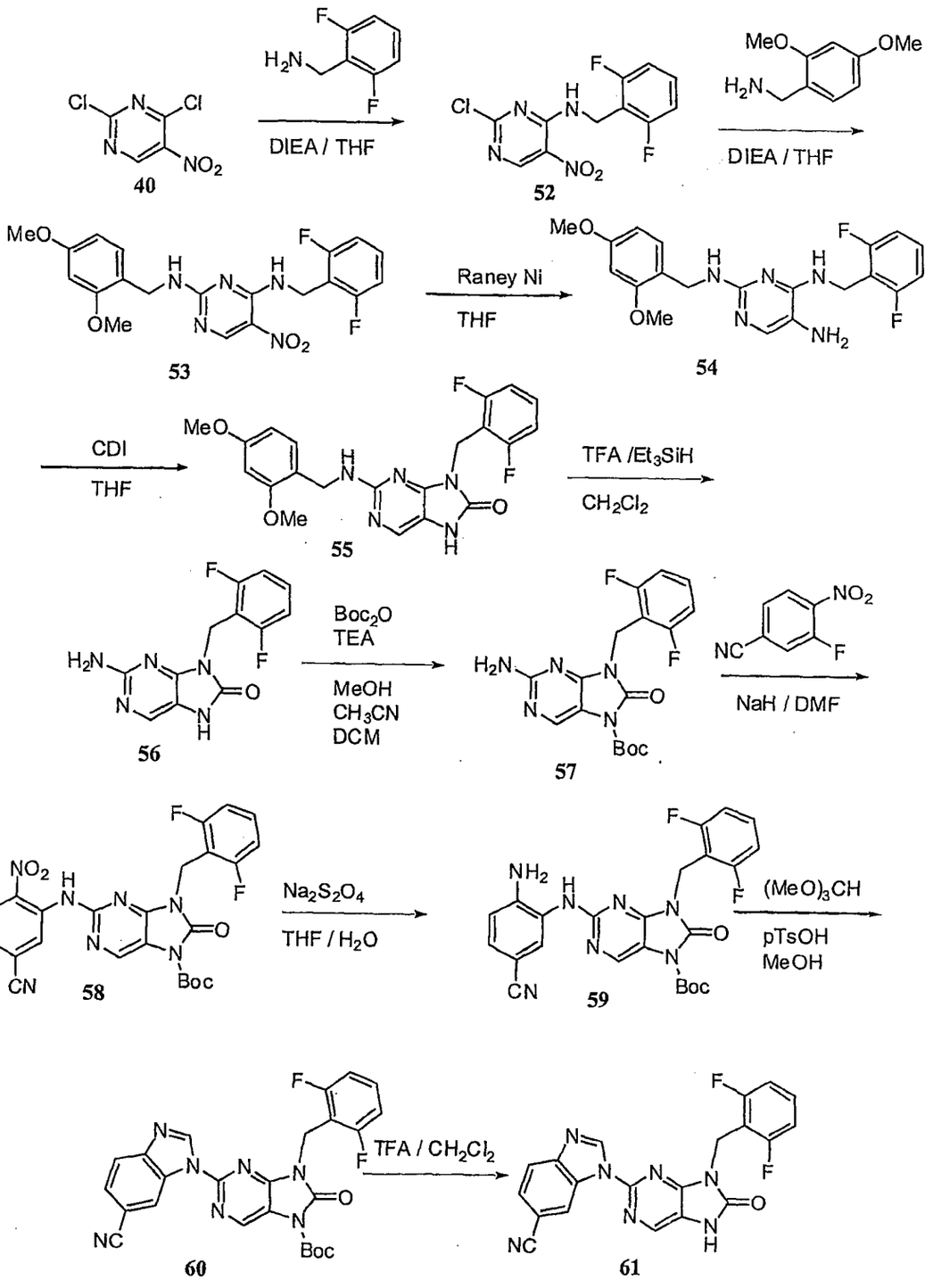
[00151] **6-(1*H*-Benzo[d]imidazol-1-il)-3-nitro-N-(piridin-3-ilmetil) piridin-2-amina (48)**. Una solución de 2,6-dicloro-3-nitropiridina (46) (0.5 g) en acetonitrilo (20 mL) se enfrió a 0°C y se trató con trietilamina (0.36 mL) seguida por 3-(aminometil)piridina (0.26 mL). La mezcla se agitó durante 30 minutos a 0 °C y ocho horas a temperatura de la sala. La solución resultante, que contenía el intermedio 6-cloro-3-nitro-N-(piridin-3-ilmetil)piridin-2-amina (47), se transfirió a un tubo sellado que contenía benzimidazol (0.84 g) y carbonato de potasio (3 g) y se calentó a 70 °C durante 16 horas. La mezcla se enfrió y se filtró. El precipitado se lavó con agua y se secó con aire para proporcionar 239 mg del compuesto del título (48).

[00152] 5-(1*H*-Benzo[d]imidazol-1-il)-3-(piridin-3-ilmetil)-1H-imidazo [4,5-b]piridin-2(3H)-ona (50) y 5-(1*H*-benzo[d]imidazol-1-il)-3-(piridin-3-ilmetil)-3H-imidazo[4,5-b]piridina (**51**). Una solución de 6-(1*H*-benzo[d]imidazol-1-il)-3-nitro-N-piridin-3-ilmetil)piridin-2-amina (48) (50 mg) en 1 mL de DMSO se trató con una solución de $Na_2S_2O_4$ (300 mg) en 1 mL de agua. La mezcla se agitó durante dos horas y se diluyó con 50 mL de acetato de etilo. La mezcla se lavó tres veces con alícuotas de 50 mL de

solución de cloruro de sodio saturado, se secó sobre sulfato de sodio, se filtró y se concentró *in vacuo* para proporcionar el intermedio 6-(1*H*-benzo[d]imidazol-1-il)-N2-(piridin-3-ilmetil)piridin-2,3-diamina (**49**). La mitad del intermedio se disolvió en cloruro de metileno (2 mL) y se trató con 1,1'-carbonildiimidazol (46 mg) a temperatura de la sala durante 16 horas. La mezcla cruda resultante se purificó por TLC preparativa (1000 micrones, 5% MeOH / CH_2Cl_2) para proporcionar 7.1 mg de 5-(1*H*-benzo[d]imidazol-1-il)-3-(piridin-3-ilmetil)-1H-imidazo[4,5-b]piridin-2(3H)-ona (50): ^{1}H-NMR ($CDCl_3$) δ 10.0 (br s, 1H), 8.9 (s, 1H), 8.6 (d, 1H), 8.5 (s, 1H), 7.9 (m, 2H), 7.8 (m, 1H), 7.6 (d, 1H), 7.4 (m, 2H), 7.4 (m, 1H), 7.3 (d, 1H), 5.2 (s, 2H). La otra mitad del intermedio reducido se disolvió en 1 mL de ácido fórmico y se calentó en un microondas a 220 °C durante 10 minutos. La mezcla se concentró *in vacuo*, se diluyó con cloruro de metileno, y se lavó con solución de bicarbonato de sodio acuoso saturado. La capa orgánica se separó, se secó con sulfato de sodio, se filtró y se concentró *in vacuo*.

[00153] Purificación por TLC preparativa (1000 micrones, 5% MeOH / CH_2Cl_2) proporcionó 3.5 mg de 5-(1*H*-benzo[d]imidazol-1-il)-3-(piridin-3-ilmetil)-3H-imidazo[4,5-b]piridina (**51**): ^{1}H-NMR ($CDCl_3$) δ 8.8 (s, 1H), 8.6 (d, 1H), 8.6 (s, 1H), 8.3 (d, 1H), 8.2 (s, 1H), 8.0 (m, 1H), 7.9 (m, 1H), 7.7 (dd, 1H), 7.6 (d, 1H), 7.4 (m, 2H), 7.3 (m, 1H).

[00154] Ejemplo 20: Síntesis regioespecífica: Síntesis de 3-(9-(2,6-Difluorobencil)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[*d*]imidazol-5-carbonitrilo



[00155] ***N*²-(2,4-Dimetoxibencil)-*N*⁴-(2,6-difluorobencil)-5-nitropirimidin-2,4-diamina (53).** 2,6-Difluorobencilamina (0.24 mL) se agregó gota a gota durante 1 minuto a una solución de 2,4-dicloro-5-nitropirimidina (40) (0.388 g) y DIEA (0.77 mL) en THF en un baño frío puesto a -78°C. La mezcla de reacción se agitó durante 15 minutos más a -78°C, luego se retiró del baño frío y se dejó calentar a temperatura de la

sala. Se agregó más DIEA (0.77 mL) al intermedio de reacción (*N*-(2,6-difluorobencil)-2-cloro-5-nitropirimidin-4-amina) (**52**) seguido por la adición de 2,4-dimetoxibencilamina (0.30 mL) y la mezcla resultante se agitó a temperatura de la sala de un día para otro. La purificación mediante cromatografía en columna (eluida con 1 y 2.5 % MeOH/DCM) produjo N^2-(2,4-dimetoxibencil)-N^4-(2,6-difluorobencil)-5-nitropirimidin-2,4-diamina (**53**) (0.80 g), $MH^+ = 432$.

[00156] 2-(2,4-Dimetoxibencilamino)-9-(2,6-difluorobencil)-7*H*-purin-8(9*H*)-ona (55). Níquel de Raney se agregó a una solución de N^2-(2,4-dimetoxibencil)-N^4-(2,6-difluorobencil)-5-nitropirimidin-2,4-diamina (0.80 g) en THF (50 mL) bajo enjuague de argón. Se vació la suspensión, se cargó con hidrógeno (balón) y se agitó durante 16 horas. La mezcla resultante se filtró a través de un tapón de celita que se enjuagó exhaustivamente con THF y MeOH para proporcionar N^2-(2,4-dimetoxibencil)-N^4-(2,6- difluorobencil)pirimidin-2,4,5-triamina (54), que se usó tal como estaba en la siguiente reacción.

[00157] Carbonildiimidazol (0.93 g) se agregó a una solución de N^2-(2,4-dimetoxibencil)-N^4-(2,6-difluorobencil)pirimidin-2,4,5-triamina (**54**) en THF (20 mL) y la mezcla resultante se agitó a temperatura de la sala de un día para otro, luego se retiraron los disolventes bajo presión reducida y se tomaron en EtOAc y se lavaron dos veces con agua. Los orgánicos se secaron, se filtraron y se evaporaron y se purificaron mediante cromatografía en columna, elución con 2.5 y 4 % MeOH/DCM, para proporcionar 2-(2,4-dimetoxibencilamino)-9-(2,6-difluorobencil)-7*H*-purin-8(9*H*)-ona (**55**) (0.58 g), $MH^+ = 428$.

[00158] *terc*-Butil 9-(2,6-difluorobencil)-2-amino-8-oxo-8,9-dihidropurin-7-carboxilato (57). Una solución 1:1 de TFA/DCM (10 mL) se agregó a 2-(2,4-dimetoxibencilamino)-9-(2,6-difluorobencil)-7*H*-purin-8(9*H*)-ona (**55**) (0.58 g) y se agitó durante 30 minutos, después de los

cuales se agregó trietilsilano (2 mL) y la mezcla se agitó 4 horas más. Los disolventes se retiraron *in vacuo*, el residuo se tomó en una cantidad mínima de MeOH y se trituró con Et_2O, para proporcionar la sal TFA de 9-(2,6-difluorobencil)-2-amino-7*H*-purin-8(9*H*)-ona (**56**) (0.55 g), MH^+ = 278, como un sólido color salmón.

[00159] 9-(2,6-Difluorobencil)-2-amino-7*H*-purin-8(9*H*)-ona (0.55 g) se disolvió en una mezcla de MeOH/ACN/DCM (40 mL), se agregaron Et_3N (2 mL) y di-*terc*-butil dicarbonato (0.61 g) y la mezcla se agitó a temperatura de la sala de un día para otro. Los disolventes de la reacción se retiraron y el material crudo se tomó en DCM y se lavó con H_2O, se evaporó y se purificó mediante cromatografía en columna, elución con 2 y 3 % MeOH/DCM suministró el producto del título (**57**) (0.36 g), MH^+ = 378, MH^+-BoC = 278 (mayor), $(M + Na)^+$ = 400 y $(2M + Na)^+$ = 777 se observaron también.

[00160] ***terc*-Butil 9-(2,6-difluorobencil)-2-(5-ciano-2-nitrofenilamino)-8-oxo-8,9-dihidropurin-7-carboxilato (58).** Se agregó hidruro de sodio (88 mg, 95%), bajo enjuague de argón, a una solución de *terc*-butil 9-(2,6-difluorobencil)-2-amino-8-oxo-8,9-dihidropurin-7-carboxilato (**57**) (191 mg) y 3-fluoro-4-nitrobenzonitrilo (415 mg) en DMF (5 mL) a -40 °C. La mezcla de reacción se dejó calentar a -20 °C durante 3 horas, luego se extinguió mediante la adición de NH_4Cl acuoso saturado; una vez a temperatura de la sala la mezcla se diluyó con EtOAc y se separó. Los orgánicos se lavaron con salmuera (3 x), se secaron, se filtraron y se evaporaron, se purificaron mediante cromatografía en columna, (eluida con DCM y 1 y 2.5 % MeOH/DCM) para proporcionar *terc*-Butil 9-(2,6-difluorobencil)-2-(5-ciano-2-nitrofenilamino)-8-oxo-8,9-dihidropurin-7-carboxilato (58) (288 mg), MH^+ = 524.

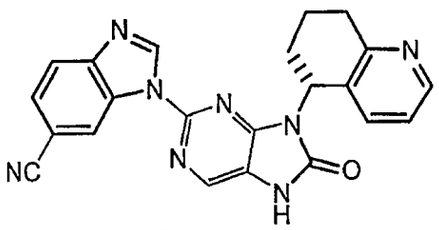
[00161] ***terc*-Butil 9-(2,6-difluorobencil)-2-(6-ciano-1*H*-benzo[*d*] midazol-1-il)-8-oxo-8,9-dihidropurin-7-carboxilato (60).** Una solución

recién preparada de hidrosulfito de sodio (téc., 1 g) y bicarbonato de sodio (0.5 g) en H_2O (10 mL) se agregó a una solución del compuesto nitro anterior (**58**) (288 mg) en THF (10 mL). La mezcla se agitó vigorosamente durante 5 minutos, se extrajo con DCM (3 x); los orgánicos combinados se lavaron con salmuera, se secaron, se filtraron y se concentraron para producir el intermedio *terc*-butil 9-(2,6-difluorobencil)-2-(2-amino-5-cianofenilamino)-8-oxo-8,9-dihidropurin-7-carboxilato (**59**), que se utilizó tal como estaba en el siguiente paso.

[00162] Una cantidad catalítica de monohidrato de ácido *para*-toluenosulfónico se agregó a una solución del intermedio amina anterior y ortoformiato de trimetilo (3 mL) en MeOH (10 mL). Después de 1 hora, el material crudo se adsorbió en gel de sílice y se purificó por cromatografía en columna (eluida con 1 y 2 % MeOH/DCM) para proporcionar *terc*-Butil 9-(2,6-difluorobencil)-2-(6-ciano-1H-benzo[*d*]imidazol-1-il)-8-oxo-8,9-dihidropurin-7-carboxilato (60) (164 mg), MH^+ = 504 y MH^+-BOC = 404.

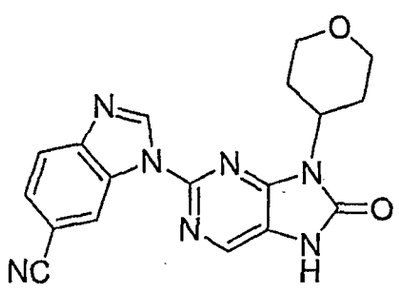
[00163] 3-(9-(2,6-Difluorobencil)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3*H*-benzo[*d*]imidazol-5-carbonitrilo (61). Una solución 1:1 de TFA/DCM (10 mL) se agregó a *terc*-Butil 9-(2,6-difluorobencil)-2-(6-ciano-1*H*-benzo[*d*]imidazol-1-il)-8-oxo-8,9-dihidropurin-7-carboxilato (**60**) y se agitó durante 1 hora. Los disolventes se retiraron *in vacuo* y el sólido resultante se trituró con Et_2O, y se suspendió en 6N HCl. El retiro de los disolventes y la trituración con Et_2O del sólido resultante produjeron el compuesto del título (**61**) (68 mg) como una sal HCl, MH^+ = 404, ^1H NMR (d_6-DMSO) δ 11.8 (s, 1H), 9.2 (s, 1H), 8.8 (s, 1H), 8.0 (s, 1H), 7.9 (d, 1H), 7.8 (s ancho, 1H), 7.4 (d, 1H), 7.4 (quintete, 1H), 7.1 (m, 2H), 5.2 (s, 2H) ppm, ^{19}F NMR δ -114.3 (m).

[00164] Síntesis de 3-(8-Oxo-9-((*R*)-5,6,7,8-tetrahidroquinolin-5-il)-8,9-dihidro-7*H*- purin-2-il)-3*H*-benzo[*d*]imidazol-5-carbonitrilo.



[00165] El compuesto del título se sintetizó de (*R*)-5,6,7,8-tetrahidroquinolin-5-amina (obtenida mediante resolución de Novozyme 435 (J. Org. Chem., **2003**, 68, 3546) en una manera similar a la descrita en Ejemplo 29) mediante el procedimiento descrito en Ejemplo 20. ^{1}H-NMR (300 MHz, $CDCl_3$+5% CD_3OD) δ 8.9 (br s, 1H), 8.7 (s, 1H), 8.6 (m, 1H), 8.3 (s, 1H), 7.8 (d, 1H), 7.7 (d, 2H), 7.6 (d, 1H), 7.5 (dd, 1H), 5.9 (dd, 1H), 3.3 (m 2H), 2.7-2.5 (m, 1H), 2.4-2.2 (m, 2H), 2.1-2.0 (m, 1H); MH^+ = 386409.

[00166] Ejemplo 21: Síntesis de 3-(8-Oxo-9-(tetrahidro-2H-piran-4-il)-8,9-dihidro-7H-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo (62).

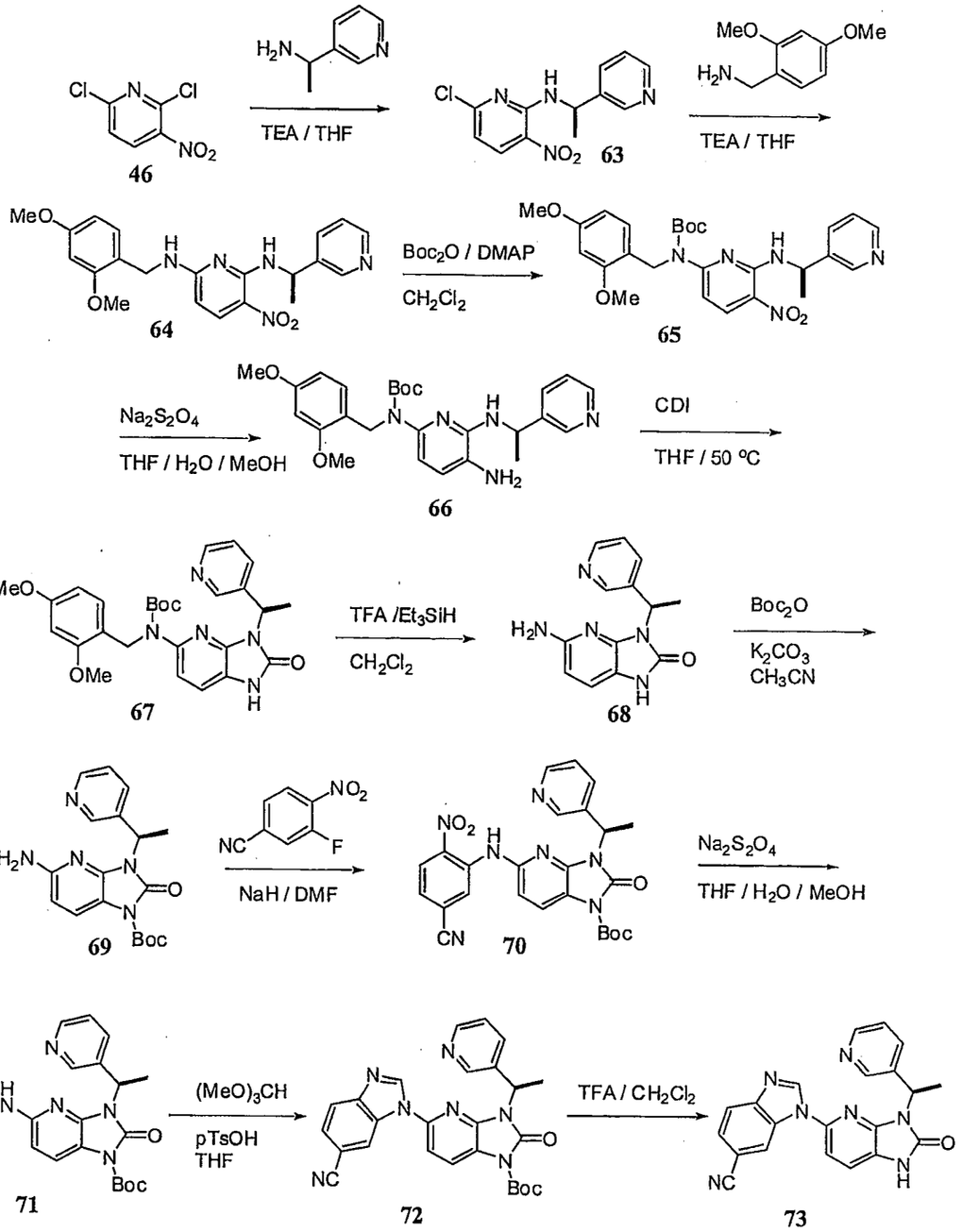


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[00167] El compuesto del título puede sintetizarse utilizando el mismo procedimiento como se describe para la síntesis de 3-(9-(2,6-difluorobencil)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3*H*-benzo[*d*]imidazol-5-carbonitrilo (**61**, Ejemplo 20).

[00168] ^{1}H NMR (d_6-DMSO) 11.71 (s, 1H), 9.34 (s, 1H), 8.94 (d, J = 1.5 Hz, 1H), 8.38 (s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.79 (dd, J = 8.1, 1.5 Hz, 1H), 4.57 (m, 1H), 4.04 (m, 2H), 3.50 (m, 2H), 2.59 (m, 2H), 1.79 (m, 2H); masa (MH+) 362.1.

[00169] Ejemplo 22: Síntesis regioespecífica de un derivado de oxoimidazopiridina: Síntesis de 3-(2-oxo-3-((R)-1-(piridin-3-il)etil)-2,3-dihidro-1H-imidazo[4,5-b]piridin-5-il)-3H-benzo[d]imidazol-5-carbonitrilo.



[00170] **(R)-N6-(2,4-Dimetoxibencil)-3-nitro-N2-(1-(piridin-3-il)etil) piridin-2,6-diamina (64).** Una solución de 2,6-dicloro-5-nitropiridina (**46**) (0.5 g) en THF (20 ml) se enfrió a 0 °C y se trató con 1.6 mL trietilamina seguida por (R)-1-piridin-3-il-etilamina (300 µL). La mezcla se agitó durante 1.5 horas, luego se calentó a temperatura de la sala y se agitó otras 20 horas. Se agregó 2,4-dimetoxibencilamina (0.8 mL) y la mezcla se

calentó a 50 °C durante cuatro horas. La mezcla se diluyó con acetato de etilo y se lavó dos veces con solución de cloruro de sodio saturado. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y se concentró. Cromatografía en columna (50 → 100% acetato de etilo en hexanos) proporcionó 761 mg de (R)-N6-(2,4-Dimetoxibencil)-3-nitro-N2-(1-(piridin-3-il)etil)piridin-2,6-diamina (64).

[00171] (R)-*terc*-Butil 2,4-dimetoxibencil(5-nitro-6-(1-(piridin-3-il) etilamino)piridin-2-il)carbamato (65). Una solución de (R)-N6-(2,4-dimetoxibencil)-3-nitro-N2-(1-(piridin-3-il)etil)piridin-2,6-diamina (**64**) (367 mg) en cloruro de metileno (20 mL) se trató con di-*terc*-butil dicarbonato (1.0 g) y 4-dimetilaminopiridina (22 mg). La mezcla se agitó durante 16 horas y se concentró *in vacuo*. Cromatografía en columna (50 → 100% acetato de etilo en hexanos) proporcionó 500 mg de (R)-*terc*-Butil 2,4-dimetoxibencil(5-nitro-6-(1-(piridin-3-il)etilamino)piridin-2-il) carbamato (**65**).

[00172] (R)-*terc*-Butil 2,4-dimetoxibencil(2-oxo-3-(1-(piridin-3-il) etil)-2,3-dihidro-1H-imidazo[4,5-b]piridin-5-il)carbamato (67). Una solución de (R)-*terc*-butil 2,4-dimetoxibencil(5-nitro-6-(1-(piridin-3-il) etilamino) piridin-2-il)carbamato (500 mg) en THF (25 mL) se trató con una solución acuosa compuesta por 2 g de $Na_2S_2O_4$ y 1 g $NaHCO_3$ en 20 mL de agua, seguida por 1 mL de metanol. La mezcla se agitó durante 30 minutos, luego se diluyó con acetato de etilo y se lavó con solución de cloruro de sodio saturado. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y se concentró para proporcionar el intermedio (R)-*terc*-butil 2,4-dimetoxibencil(5-amino-6-(1-(piridin-3-il)etilamino)piridin-2-il)carbamato (66). El intermedio se disolvió en THF (50 mL) y se trató con 1,1'-carbonildiimidazol (0.5 g) a 50 °C durante 20 horas. La mezcla se concentró y se purificó por cromatografía en columna (2 → 5% MeOH en cloruro de metileno) para proporcionar 413 mg de (R)-*terc*-Butil 2,4-

dimetoxibencil(2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidro-1H-imidazo[4,5-b]piridin- 5-il)carbamato (**67**).

[00173] (R)-*terc*-Butil 5-amino-2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (69). Una solución de (R)-*terc*-butil 2,4-dimetoxibencil(2-oxo-3-(1-piridin-3-il)etil)-2,3-dihidro-1H-imidazo[4,5-b]piridin-5-il)carbamato en cloruro de metileno (15 mL) se trató con TFA (15 mL) y trietilsilano (1.0 mL) durante una hora. La mezcla se concentró para proporcionar el intermedio (R)-5-amino-3-(1-(piridin-3-il)etil)-1H-imidazo[4,5-b]piridin-2(3H)-ona (**68**), la cual se disolvió en acetonitrilo (50 mL) y se agitó vigorosamente con di-*terc*-butil dicarbonato (1.0 g) y carbonato de potasio (3.0 g) durante 2 horas. Se agregaron cloruro de metileno (200 mL) y agua (100 mL), y la capa orgánica se separó. La capa acuosa se extrajo con otros 100 mL de cloruro de metileno. Las capas orgánicas combinadas se separaron, se secaron sobre sulfato de sodio, se filtraron y se concentraron. Cromatografía en columna (2 → 3 → 4% MeOH en cloruro de metileno) proporcionó 235 mg de (R)-*terc*-Butil 5-amino-2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (69).

[00174] (R)-*terc*-Butil 5-(5-ciano-2-nitrofenilamino)-2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (**70**). Una solución de (R)-*terc*-butil 5-amino-2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (94 mg) y 3-fluoro-4-nitrobenzonitrilo (225 mg) en DMF (6 mL) se enfrió a -25 °C y se trató con NaH (60% p/p en aceite mineral, 75 mg) y se dejó calentar lentamente a -15 °C. La mezcla se agitó durante 4 horas entre -20 °C y -15 °C, luego se diluyó con EtOAc y se extinguió con solución de cloruro de amonio saturado. La fase orgánica se lavó tres veces con salmuera, se separó, se secó sobre sulfato de sodio, se filtró y se concentró. Cromatografía en columna (2% MeOH en cloruro de metileno) proporcionó 100 mg de (R)-

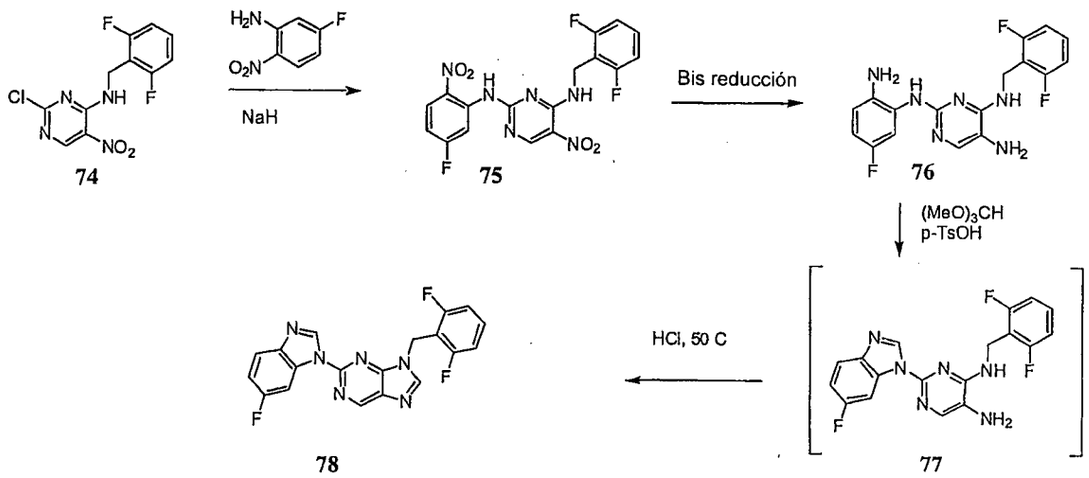
terc-Butil 5-(5-ciano-2-nitrofenilamino)-2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (**70**).

[00175] *terc*-Butil 5-(6-ciano-1H-benzo[d]imidazol-1-il)-2-oxo-3-((R)-1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (**72**). Una solución de (R)-*terc*-butil 5-(5-ciano-2-nitrofenilamino)-2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (**70**) (100 mg) en THF (5 mL) se trató con una solución acuosa compuesta por 0.5 g de $Na_2S_2O_4$ y 0.25 g $NaHCO_3$ en 5 mL de agua. La mezcla pasó rápidamente de un color rojo a un color ligeramente amarillo, lo cual indicó la reducción del grupo nitro. La mezcla se diluyó con acetato de etilo y se lavó con solución de cloruro de sodio saturado. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y se concentró para proporcionar el intermedio (R)-*terc*-butil 5-(2-amino-5-cianofenilamino)-2-oxo-3-(1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (**71**). El intermedio se disolvió en THF (5 mL), DMF (1 mL), y trimetilortoformiato (2 mL). La mezcla se trató con 10 mg de ácido p-toluenosulfónico y se agitó durante 20 horas. La mezcla se diluyó con acetato de etilo y se lavó una vez con bicarbonato de sodio saturado y dos veces con solución de NaCl saturado. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y se concentró. Cromatografía en columna (2% MeOH en cloruro de metileno) proporcionó 57 mg de *terc*-Butil 5-(6-ciano-1H-benzo[*d*]imidazol-1-il)-2-oxo-3-((R)-1-(piridin-3-il)etil)-2,3-dihidroimidazo [4,5-b]piridin-1-carboxilato (**72**).

[00176] 3-(2-Oxo-3-((R)-1-(piridin-3-il)etil)-2,3-dihidro-1*H*-imidazo [4,5-b]piridin-5-il)-3*H*-benzo[d]imidazol-5-carbonitrilo (73). Una solución de *terc*-butil 5-(6-ciano-1H-benzo[d]imidazol-1-il)-2-oxo-3-((R)-1-(piridin-3-il)etil)-2,3-dihidroimidazo[4,5-b]piridin-1-carboxilato (**72**) (57 mg) en cloruro de metileno (1 mL) se trató con TFA (1 mL) durante una hora. La mezcla se concentró y la sal TFA resultante se convirtió en la sal HCl disolviéndola en 5 mL EtOH y agregando 0.5 mL de HCl concentrado,

luego se concentró la solución *in vacuo*. El proceso se repitió, y el residuo resultante se disolvió en una cantidad mínima de metanol y se trituró con la adición de éter etílico. Luego de 3 trituraciones, se aisló sal HCl (39 mg) de 3-(2-oxo-3-((R)-1-(piridin-3-il)etil)-2,3-dihidro-1H-imidazo[4,5-b]piridin-5-il)-3H-benzo[d]imidazol-5-carbonitrilo (73) como un sólido de color café claro: ^{1}H-NMR (CD_3OD) δ 9.9 (br s, 1H), 9.2 (s, 1H), 9.0 (m, 2H), 8.5 (s, 1H), 8.3 (m, 1H), 8.2 (m, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 6.3 (q, 1H), 2.3 (d, 3H).

[00177] Ejemplo 23: Síntesis regioespecífica: Síntesis de 9-(2,6-Difluorobencil)-2-(6- fluoro-1*H*-benzo[*d*]imidazol-1-il)-9*H*-purina (**78**)

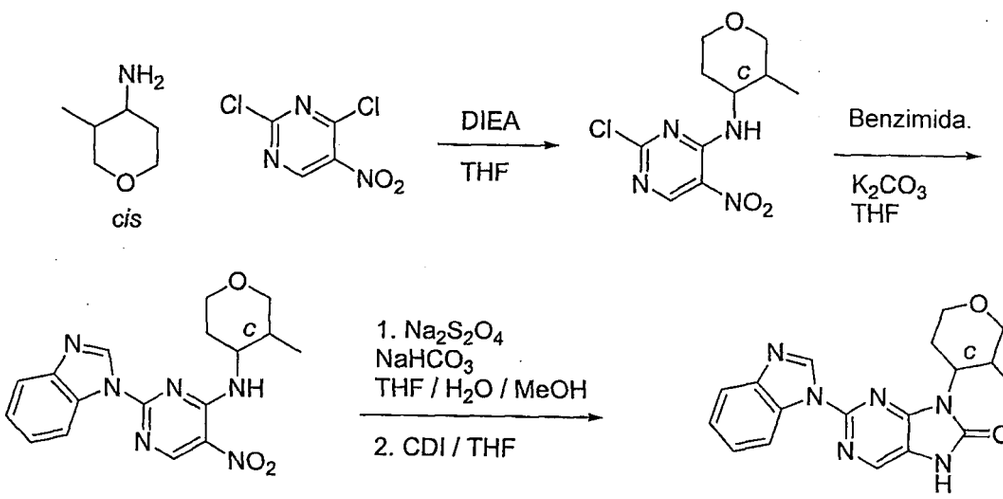


[00178] ***N*^{4}-(2,6-Difluorobencil-*N*^{2}-(5-fluoro-2-nitrofenil)-5-nitropirimidin-2,4-diamina (75)**. Bajo una atmósfera de argón, se agregó borohidruro de sodio (100 mg) a una solución de N-(2,6-difluorobencil)-2-cloro-5-nitropirimidin-4-amina (150 mg) y 5-fluoro-2-nitroanilina (78 mg) en THF (10 mL) a temperatura de la sala. La mezcla se agitó durante 30 minutos, se extinguió mediante la adición de NH_4Cl acuoso saturado, se extrajo con DCM y se purificó por HPLC preparativa para producir un bajo rendimiento de N^4-(2,6-difluorobencil)-*N*^{2}-(5-fluoro-2-nitrofenil)-5-nitropirimidin-2,4-diamina (**75**) (24 mg), $MH^+ = 421$.

[00179] **9-(2,6-Difluorobencil)-2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-il)-9*H*-purina (78)**. Una solución recién preparada de hidrosulfito de sodio

(téc., 100 mg) y bicarbonato de sodio (50 mg) en H_2O (5 mL) se agregó a una solución de N^4-(2,6-difluorobencil)-N^2-(5-fluoro-2-nitrofenil)-5-nitropirimidin-2,4-diamina (**75**) (24 mg) en THF (5 mL). La mezcla se agitó vigorosamente durante 30 minutos y se extrajo con DCM (3x). Los orgánicos combinados se lavaron con salmuera, se secaron, se filtraron y se concentraron para producir el intermedio N^4-(2,6-difluorobencil)-N^2-(2-amino-5-fluorofenil) pirimidin-2,4,5-triamina (**76**) para uso en el siguiente paso. Una cantidad catalítica de ácido *para*-toluenosulfónico se agregó a una solución del intermedio y ortoformiato de trimetilo (1 mL) en MeOH (2 mL); luego de 2 horas se agregó HCl concentrado (1 mL), y la mezcla se calentó a 50 °C durante 4 horas. Los disolventes de reacción se retiraron y el material crudo se purificó por HPLC preparativa para producir 9-(2,6-Difluorobencil)-2-(6-fluoro-1*H*- benzo[*d*]imidazol-1-il)-9*H*-purina (**78**) como la sal TFA en bajo rendimiento (0.8 mg) MH^+ = 404, ^{1}H NMR (5 % $CD_3OD/CDCl_3$) δ 9.1 (s, 1H), 9.0 (s, 1H), 8.3 (d, 1H), 8.2 (s, 1H), 7.6 (m, 1H), 7.0 (t, 1H), 6.9 (m, 2H), 5.5 (s, 2H) ppm, ^{19}F NMR δ-76.6 (s, TFA), -114.5 (m), - 117.1 (m).

[00180] Ejemplo 24. Síntesis de 2-(1*H*-Benzo[d]imidazol-1-il)-9-(*cis*-3-metil-tetrahidro-2H-piran-4-il)-7*H*-purin-8(9*H*)-ona.



[00181] **2-Cloro-*N*-(*cis*-3-metil-tetrahidro-2H-piran-4-il)-5-nitropirimidin-4-amina**. A una suspensión de 0.24 g de la sal clorhidrato

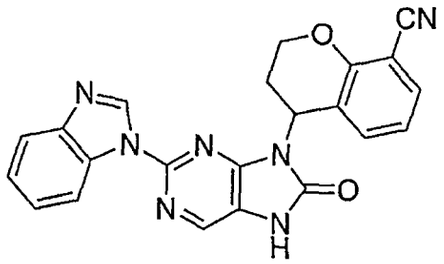
de *cis*-3-metil-tetrahidro-2H-piran-4-amina (WO 2004/041161) y DIEA (1.5 mL) en THF (10 mL) a -78 °C se agregó 2,4-dicloro-5-nitropirimidina (0.72 g). La mezcla se dejó alcanzar lentamente la temperatura de la sala y se agitó durante 16 horas. La mezcla se diluyó con EtOAc y se lavó 3 veces con salmuera. La capa orgánica se separó, se secó sobre sulfato de sodio, y se concentró *in vacuo*. Cromatografía en columna (20 → 40% EtOAc / hexanos) proporcionó 289 mg del compuesto del título.

[00182] 2-(1*H*-Benzo[d]imidazol-1-il)-N-(*cis*-3-metil-tetrahidro-2*H*-piran-4-il)-5-nitropirimidin-4-amina. A una solución de 2-cloro-N-(*cis*-3-metil-tetrahidro-2*H*-piran-4-il)-5-nitropirimidin-4-amina (115 mg) en acetonitrilo (5 mL) se agregaron carbonato de potasio (300 mg) y benzimidazol (150 mg). La mezcla se agitó a 70 °C durante 2.5 horas. Luego de diluir con 70 mL EtOAc, la mezcla se lavó con salmuera, se secó sobre sulfato de sodio, y se concentró *in vacuo*. Cromatografía en columna (50 →100% EtOAc/hexanos) proporcionó 99 mg del compuesto del título.

[00183] 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(*cis*-3-metil-tetrahidro-2H-piran-4-il)-7H-purin-8(9*H*)-ona. A una solución de 2-(1*H*-benzo[*d*]imidazol-1-il)-N-(*cis*-3-metil-tetrahidro-2*H*-piran-4-il)-5-nitropirimidin-4-amina (51 mg) en THF (10 mL) se agregaron una solución de hidrosulfito de sodio (300 mg) y bicarbonato de sodio (150 mg) en agua (10 mL). La mezcla se volvió pronto azul, luego incolora. Se agregó metanol (1 mL) para mantener la homogeneidad de la solución. La mezcla se diluyó con 70 mL EtOAc y se lavó dos veces con salmuera. Los lavados acuosos se extrajeron con otros 50 mL de EtOAc y luego las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron *in vacuo* para proporcionar 2-(1*H*-benzo[d]imidazol-1-il)-N4-(*cis*-3-metil-tetrahidro-2H-piran-4-il)pirimidin-4,5-diamina. El intermedio diamina se disolvió en THF (5 mL) y se trató con 1,1'-carbonildiimidazol (80 mg) a 50 °C durante 16 horas. La mezcla se diluyó con 50 mL EtOAc y se lavó 3 veces con salmuera. La capa orgánica se separó, se secó sobre sulfato de

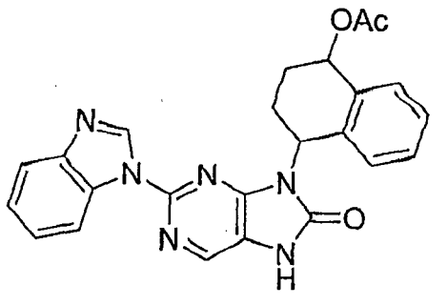
sodio, y se concentró *in vacuo*. Cromatografía en columna (2 → 4% MeOH / DCM) proporcionó 19.3 mg del compuesto del título. ^{1}H-NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 8.9 (s, 1H), 8.5 (d, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.4 (t, 1H), 7.3 (t, 1H), 4.7 (m, 1H), 4.2 (d(br), 1H), 3.9 (d, 1H), 3.7 (d, 1H), 3.5 (m, 2H), 2.3 (t(br), 1H), 1.8 (d(br), 1H), 1.2 (d, 3H).

[00184] Síntesis de 4-(2-(1*H*-Benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)-1,2,3,4-tetrahidronaftalen-1-carbonitrilo.



[00185] El compuesto del título se sintetizó de 4-amino-3,4-dihidro-2H-cromeno-8-carbonitrilo mediante el procedimiento descrito en Ejemplo 24. ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.87 (s, 1H), 8.57 (s, 1H), 7.70 (m, 3H), 7.31 (m, 3H), 6.94 (t, J = 7.8 Hz, 1H), 5.90 (m, 1H), 4.61 (m, 2H), 2.73 (m, 1H), 2.33 (m, 1H); masa (MH+) 410.1.

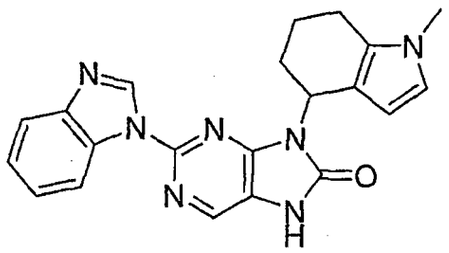
[00186] Síntesis de *cis/trans*-4-(2-(1*H*-Benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)-1,2,3,4-tetrahidronaftalen-1-il acetato.



[00187] El compuesto del título se sintetizó de 4-amino- 1,2,3,4-tetrahidronaftalen-1-il acetato mediante el procedimiento descrito en Ejemplo 24. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (s, 0.66H), 10.48 (s, 0.34H), 8.87 (s, 0.66H), 8.83 (s, 0.34H), 8.30 (s, 0.66H), 8.27 (s, 0.34H),

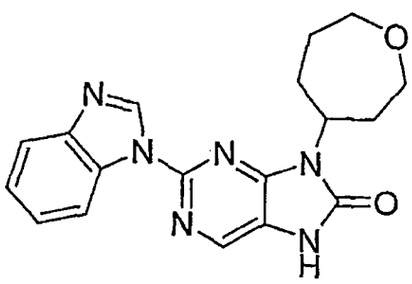
7.76-7.02 (m, 8H), 6.35 (m, 0.34H), 6.17 (m, 0.66H), 5.93 (s, 0.34H), 5.79 (m, 0.66H), 2.90-2.01 (m, 7H); masa (MH+) 441.0.

[00188] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(1-metil-4,5,6,7-tetrahidro-1*H*-indol-4-il)-7*H*-purin-8(9*H*)-ona.



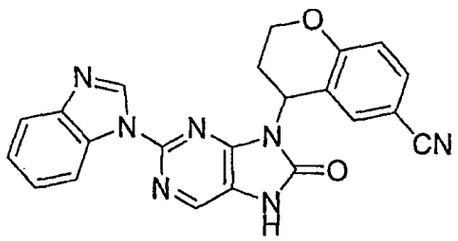
[00189] El compuesto del título se sintetizó de 1-metil-4,5,6,7-tetrahidro-1H- indol-4-amina mediante el procedimiento descrito en Ejemplo 24. ^{1}H NMR (CD_3OD) δ8.90 (s, 1H), 8.25 (s, 1H), 7.88 (m, 1H), 7.68 (m, 1H), 7.32 (m, 2H), 6.51 (d, J= 2.7 Hz, 1H), 5.66 (m, 2H), 3.65 (s, 3H), 2.80 (m, 2H), 2.46 (s, 1H), 2.19 (m, 2H), 1.96 (m, 1H); masa (MH+) 386.0.

[00190] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(oxepan-4-il)-7*H*-purin-8(9*H*)-ona.



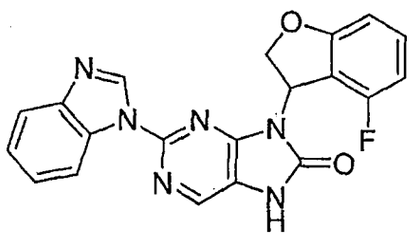
[00191] El compuesto del título se sintetizó de oxepan-4-amina mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR ($CDCl_3$) δ 9.0 (s, 1H), 8.5 (d, 1H), 8.1 (s, 1H), 7.7 (d, 1H), 7.3 (m, 2H), 4.6 (t, 1H), 3.9 (m, 2H), 3.8 (m, 2H), 2.7 (m, 2H), 2.0 (m, 4H) ppm.

[00192] Síntesis de 4-(2-(1*H*-Benzo[*d*]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)croman-6-carbonitrilo.



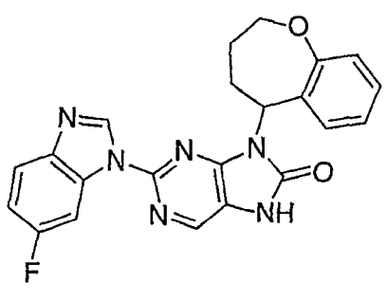
[00193] El compuesto del título se sintetizó de 4-amino-3,4-dihidro-2H-cromeno-6-carbonitrilo mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR de sal TFA (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 9.2 (s, 1H), 8.4 (s, 1H), 8.0 (d, 1H), 7.9 (d, 1H), 7.4-7.6 (m, 3H), 7.1-7.2 (m, 2H), 5.8-6.0 (m, 1H), 4.6-4.7 (m, 1H), 4.4-4.5 (m, 1H), 2.8-3.0 (m, 1H), 2.2-2.4 (m, 1H).

[00194] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(4-fluoro-2,3-dihidrobenzofuran- 3-il)-7*H*-purin-8(9*H*)-ona.



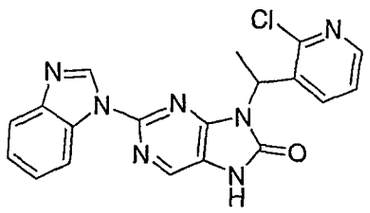
[00195] El compuesto del título se sintetizó de 4-fluoro-2,3-dihidrobenzofuran-3-amina (preparada en Ejemplo 37) mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR (300 MHz, $CDCl_3$+5%CD_3OD) δ 8.7 (s, 1H), 8.1-8.2 (m, 1H), 8.1 (s, 1H), 7.6-7.7 (m, 1H), 7.1-7.3 (m, 3H), 6.7 (d, 1H), 6.5 (d, 1H), 6.3-6.4 (m, 1H), 4.8-4.9 (m, 2H).

[00196] Síntesis de 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-(2,3,4,5-tetrahidrobenzo[*b*]oxepin-5-il)-7*H*-purin-8(9*H*)-ona.



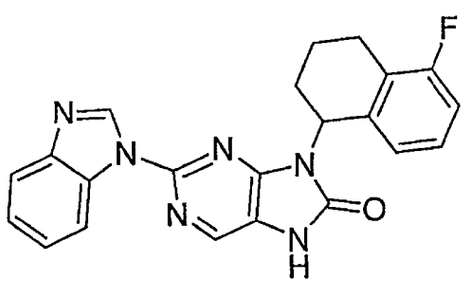
[00197] El compuesto del título se sintetizó de 2,3,4,5-tetrahidrobenzo[*b*]oxepin-5-amina (obtenida de la cetona correspondiente (J. Med. Chem., 2004, 47, 5612) utilizando los mismos procedimientos descritos para los 4-aminocromanos) mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR (300 MHz, $CDCl_3$+5%CD_3OD) δ 8.8 (s, 1H), 8.2 (s, 1H), 8.0 (dd, 1H), 7.6-7.7 (m, 1H), 6.95-7.2 (m, 3H), 6.9 (t, 1H), 6.6 (d, 1H), 5.9 (d, 1H), 4.4-4.5 (m, 1H), 3.7-3.9 (m, 1H), 2.8-3.0 (m, 1H), 2.0-2.3 (m, 3H).

[00198] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(1-(2-cloropiridin-3-il)etil)-7*H*-purin-8(9*H*)-ona.



[00199] El compuesto del título se sintetizó de 3-(α-aminoetil)-2-cloropiridina mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR ($CDCl_3$) δ 8.8 (s, 1H), 8.4 (d, 1H), 8.3 (d, 1H), 8.2 (d, 1H), 8.1 (s, 1H), 7.7 (d, 1H), 7.3 (m, 3H), 3.4 (m, 1H), 2.0 (d, 3H), ppm.

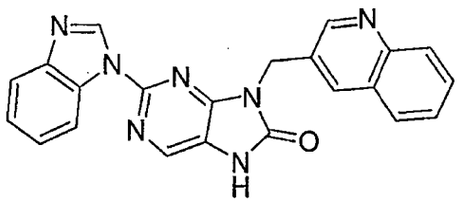
[00200] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(5-fluoro-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona.



[00201] El compuesto del título se sintetizó de 5-fluoro-1,2,3,4-tetrahidronaftalen-1-amina mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR ($CDCl_3$) δ 8.7 (s, 1H), 8.1 (s, 1H), 7.6 (d, 1H), 7.5 (d, 1H), 7.2

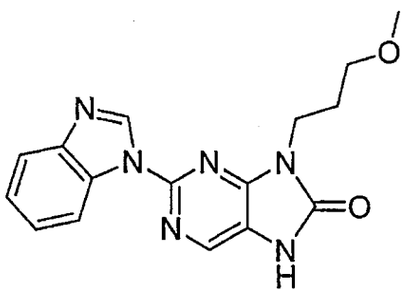
(q, 2H), 6.9 (m, 2H), 6.7 (d, 1H), 5.7 (m, 1H), 3.3 (s, 2H), 2.8 (m, 2H), 2.4 (q, 1H), 2.1 (m, 1H), 1.8 (m, 1H), ppm.

[00202] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(quinolin-3-ilmetil)-7*H*-purin- 8(9*H*)-ona.



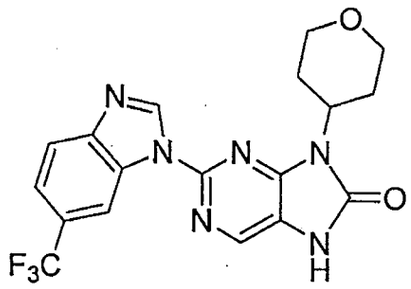
[00203] El compuesto del título se sintetizó de 3-aminometilquinolina mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR ($CDCl_3$) δ 9.8 (s, 1H), 9.4 (s, 1H), 8.9 (s, 1H), 8.6 (d, 1H), 8.3 (m, 2H), 8.1 (d, 1H), 7.9 (m, 2H), 7.8 (d, 1H), 7.5 (t, 2H), 5.5 (s, 2H) ppm.

[00204] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(3-metoxipropil)-7*H*-purin-8(9*H*)-ona.



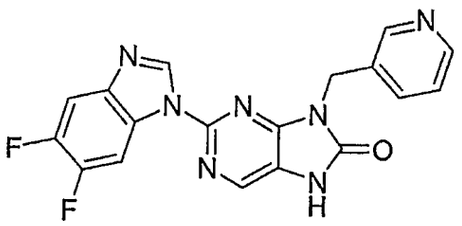
[00205] El compuesto del título se sintetizó de 3-metoxipropan-1-amina mediante el procedimiento descrito en Ejemplo 24. ^{1}H NMR (CD_3OD) 59.71 (s, 1H), 8.81 (d, 1H), 8.30 (s, 1H), 7.83 (d, 1H), 7.57 (m, 2H), 4.15 (t, 2H), 3.50 (t, 2H), 3.28 (s, 3H), 2.13 (m, 2H); MS (MH^+) 325.2.

[00206] Síntesis de 9-(Tetrahidro-2H-piran-4-il)-2-(6-(trifluorometil)-1H-benzo[d]imidazol-1-il)-7*H*-purin-8(9*H*)-ona.



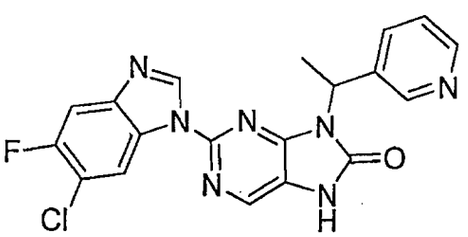
[00207] El compuesto del título se sintetizó de 3-metoxipropan-1-amina mediante el procedimiento descrito en Ejemplo 24. ^{1}H NMR (CD_3OD + $CHCl_3$) δ 9.49 (s, 1H), 9.04 (s, 1H), 8.33 (s, 1H), 7.94 (d, 1H), 7.72 (m, 1H), 4.67 (m, 1H), 4.17 (m, 2H), 3.61 (m, 2H), 2.81 (m, 2H), 1.85 (m, 2H); MS (MH^+) 405.1.

[00208] Síntesis de 2-(5,6-Difluoro-1*H*-benzo[*d*]imidazol-1-il)-9-(piridin-3-ilmetil)-7*H*-purin-8(9*H*)-ona.



[00209] El compuesto del título se sintetizó de 5,6-difluoro-1H-benzo[*d*]imidazol (Ejemplo 4) mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.2 (s, 1H), 9.0 (br, 1H), 8.7 (br, 1H), 8.6 (d, 1H), 8.4 (dd, 1H), 8.3 (s, 1H), 7.9 (dd, 1H), 7.6 (m, 2H), 5.4 (s, 2H).

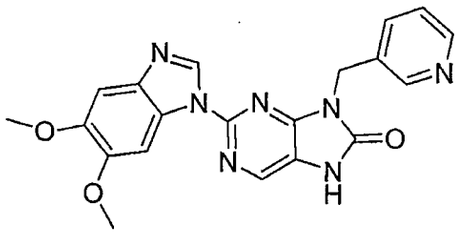
[00210] Síntesis de 2-(6-Cloro-5-fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-(1-(piridin-3-il)etil)-7*H*-purin-8(9*H*)-ona.



[00211] El compuesto del título se sintetizó de 6-cloro-5-fluorobenzimidazol mediante el procedimiento descrito en Ejemplo 24. ^{1}H-

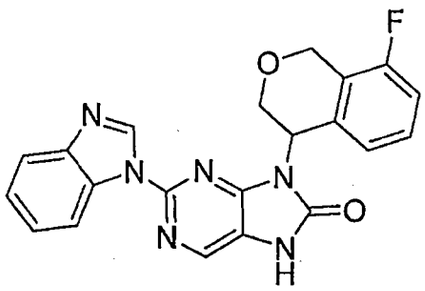
NMR (300 MHz, CD_3OD) δ 9.2 (bs, 1H), 9.0 (m, 1H), 8.9-8.5 (m, 2H), 8.4 (m, 2H), 7.9 (m, 2H), 7.7 (m, 1H), 6.2 (q, 1H), 2.2 (d, 3H).

[00212] Síntesis de 2-(5,6-Dimetoxi-1*H*-benzo[*d*]imidazol-1-il)-9-(piridin-3-ilmetil)-7*H*-purin-8(9*H*)-ona.

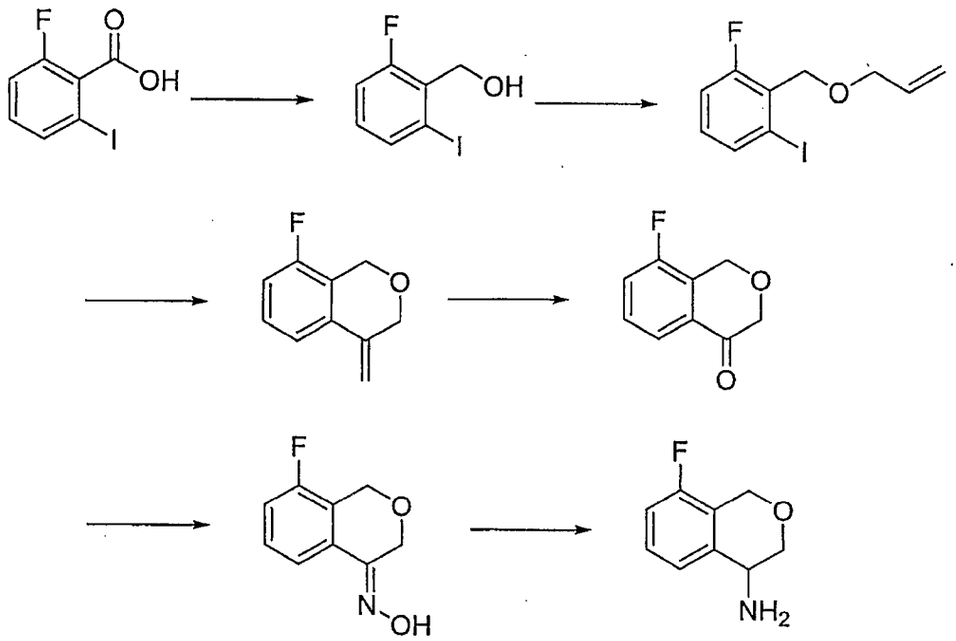


[00213] El compuesto del título se sintetizó de 5,6-dimetoxi-1H-benzo[d]imidazol mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.6 (s, 1H), 8.5 (s, 1H), 8.4 (s, 1H), 8.0 (s, 1H), 7.9 (s, 1H), 7.5 (d, 1H), 7.3 (d, 1H), 6.9 (t, 1H), 4.8 (s, 2H), 3.7 (s, 6H).

[00214] Procedimiento para la síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(8- fluoroisocroman-4-il)-7*H*-purin-8(9*H*)-ona.



[00215] 8-Fluoro-3 ,4-dihidro-1H-isocromen-4-amina.



[00216] (2-Fluoro-6-iodofenil)metanol. A una solución agitada de ácido 2-fluoro-6-yodobenzoico (10mmol) en THF (6.5mL) y borato de trimetilo (3.25mL) se agregó dimetilsulfuro de borano (12mmol) lentamente, manteniendo la temperatura interna a 20-25 °C. Se continuó la agitación durante 16 horas más a temperatura de la sala y luego se agregó metanol (1.44mL) cuidadosamente. La solución resultante se evaporó *in vacuo* para ofrecer 2.5 g del compuesto del título como un aceite amarillo pálido.

[00217] 2-(Aliloximetil)-1-fluoro-3-yodobenceno. A una solución de (2-fluoro-6-iodofenil)metanol (10 mmol) en 50 mL de THF se agregó NaH (12 mmol) en porciones pequeñas a temperatura de la sala. Luego de la adición, se agregó lentamente cromuro de alilo (12 mmol) mediante jeringa. La mezcla de reacción se agitó 16 horas a temperatura de la sala. La mezcla heterogénea blanca resultante se extinguió con agua y luego se diluyó con 100 mL de Et_2O, seguida por lavado con agua y salmuera. La capa orgánica se secó sobre $MgSO_4$ y luego se concentró a sequedad *in vacuo* para ofrecer 2.8g del compuesto del título.

[00218] 8-Fluoro-4-metilen-3,4-dihidro-1H-isocromeno. 2-(Aliloximetil)-1-fluoro-3-yodobenceno (1g) se disolvió en 20mL de CH_3CN

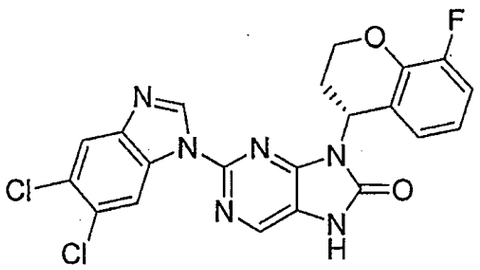
y 2.4 mL de Et_3N. La solución de reacción se desgasificó en vacío tres veces, seguida por la adición de $Pd(OAc)_2$ (37.6mg) y PPh_3 (89.8mg). La mezcla resultante se calentó a 80 °C durante 16 horas. La mezcla de reacción se enfrió a temperatura de la sala y se diluyó con Et_2O. La capa orgánica se lavó con 1N HCl, 10% $NaHCO_3$ acuoso, salmuera, y luego se secó sobre Na_2SO_4. Luego de la filtración, el filtrado se concentró a sequedad para ofrecer un aceite marrón, el cual se purificó por cromatografía instantánea para ofrecer 200 mg del compuesto del título.

[00219] 8-Fluoro-1H-isocromen-4(3H)-ona. 8-Fluoro-4-metilen-3,4-dihidro-1H-isocromeno (400 mg) se disolvió en una solución de 1:1 MeOH/DCM (50 mL) y se agregó 1mL de piridina. La mezcla se enfrió a -78 °C y se hizo burbujear ozono a través de la mezcla durante 40 minutos. La reacción se monitoreó por TLC. La mezcla se purgó con nitrógeno a -78 °C durante 10 minutos y luego se trató con PPh_3. Luego de la concentración, el residuo resultante se purificó por TLC preparativa para ofrecer 300 mg del compuesto del título.

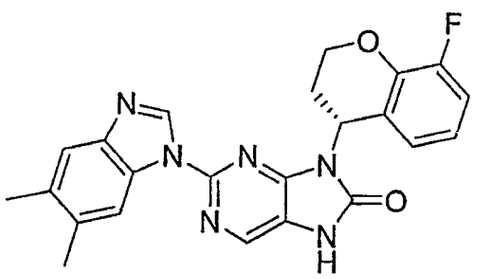
[00220] 8-Fluoro-3,4-dihidro-1H-isocromen-4-amina. El compuesto del título se preparó de 8-fluoro-1H-isocromen-4(3H)-ona mediante el procedimiento descrito en Ejemplo 29. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.4 (m, 1H), 7.3 (d, 1), 7.2 (m, 1H), 5.0 (d, 1H), 4.7 (d, 1H), 4.4 (s, 1H), 4.2 (d, 1H) 3.9 (d, 1H) ppm.

[00221] 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(8-fluoroisocroman-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de 8-fluoroisocroman-4-amina mediante el procedimiento descrito en Ejemplo 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.7 (bs, 1H), 8.2 (s, 1H), 7.6 (m, 2H), 7.3-6.9 (m, 4H), 6.8 (d, 1H), 5.8 (t, 1H), 5.0 (s, 2H), 4.2 (m, 2H).

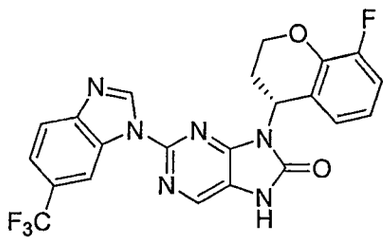
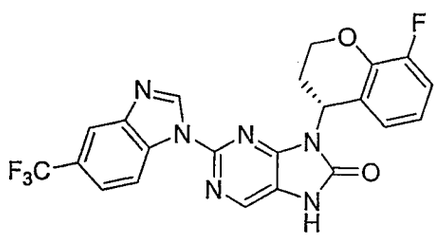
[00222] Ejemplo 25.



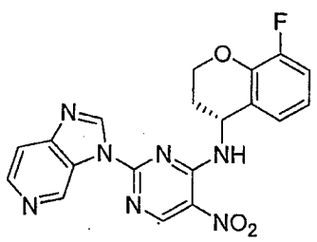
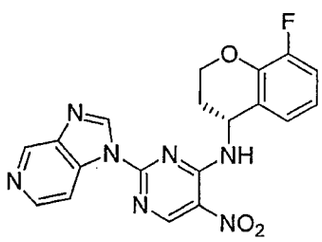
[00223] 2-(5,6-Dicloro-1H-benzo[d]imidazol-1-il)-9-((R)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona. Una solución de (R)-2-cloro-N-(8-fluorocroman-4-il)-5-nitropirimidin-4-amina en acetonitrilo se trató con 5,6-diclorobenzimidazol y carbonato de potasio. La mezcla se agitó a reflujo durante 6 horas, se enfrió a temperatura de la sala, se diluyó con 150 mL de EtOAc, y se lavó dos veces con porciones de 30 mL de agua. La capa orgánica se separó, se secó con sulfato de magnesio, se filtró y se concentró *in vacuo*. La purificación por cromatografía en columna (2% MeOH/DCM) produjo el intermedio nitropirimidinamina. El compuesto del título se sintetizó del intermedio nitropirimidinamina mediante los procedimientos descritos en Ejemplo 24. ^{1}H- NMR (300 MHz, $CDCl_3$) δ 8.7 (s, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.8 (t, 1H), 7.0 (t, 1H), 6.6 (m, 2H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 3.0 (m, 1H), 2.3 (m, 1H).



[00224] 2-(5,6-Dimetil-1H-benzo[d]imidazol-1-il)-9-((R)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de 5,6-diclorobenzimidazol mediante los procedimientos descritos en Ejemplo 25. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.6 (s, 1H), 8.8 (s, 1H), 8.3 (s, 1H), 8.0 (s, 1H), 7.6 (s, 1H), 7.0 (t, 1H), 6.7 (m, 1H), 5.9 (t, 1H), 4.7 (m, 1H), 4.5 (m, 1H), 3.2 (m, 2H), 2.4 (d, 6H).

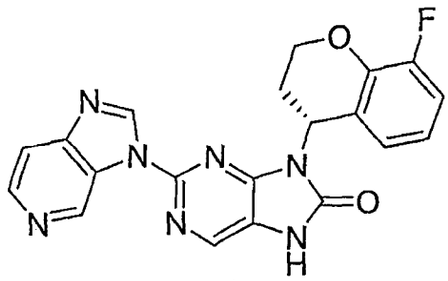



[00225] 9-((R)-8-Fluorocroman-4-il)-2-(6-(trifluorometil)-1H-benzo[d] imidazol-1-il)-7*H*-purin-8(9*H*)-ona y 9-((R)-8-fluorocroman-4-il)-2-(5-(trifluorometil)-1H-benzo[d]imidazol-1-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de 5-trifluorometilbenzimidazol (US 2004/0087601) mediante los procedimientos descritos en Ejemplo 25. Purificación por cromatografía en columna (2% MeOH/DCM) eluyó primero el 6-trifluorometil isómero (1*H*-NMR (300 MHz, $CDCl_3$) δ 8.8 (d, 2H), 8.4 (s, 1H), 7.9 (d, 1H), 7.6 (d, 2H), 7.0 (t, 1H), 6.7 (m, 2H), 5.9 (t, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 3.0 (m, 1H), 2.4 (m, 1H), seguido por el 5-trifluorometil isómero (1*H*- NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.4 (s, 1H), 8.1 (s, 1H), 8.0 (d, 1H), 7.6 (d, 2H), 7.0 (m, 1H), 6.8 (m, 2H), 5.9 (t, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 2.9 (m, 1H), 2.4 (m, 1H).

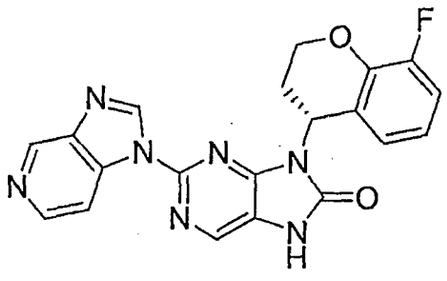



[00226] N-((R)-8-Fluorocroman-4-il)-2-(3H-imidazo[4,5-c]piridin-3-il)-5-nitropirimidin-4-amina y N-((R)-8-fluorocroman-4-il)-2-(1*H*-imidazo [4,5-c]piridin-1-il)-5-nitropirimidin-4-amina. El compuesto del título se sintetizó de 5-azabenzimidazol mediante el procedimiento descrito en Ejemplo 25. Purificación por cromatografía en columna (1% MeOH / DCM) proporcionó N-((R)-8-fluorocroman-4-il)-2-(3H-imidazo[4,5-c]piridin-3-il)-5-nitropirimidin-4-amina como el primer isómero eluyente: (^{1}*H*-NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H), 9.4 (s, 1H), 9.2 (s, 1H), 8.9 (d, 1H), 8.6 (d, 1H), 7.8 (d, 1H), 7.1 (m, 2H), 6.9 (m, 1H), 5.8 (q, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.6 (m, 1H), 2.4 (m, 1H).). N-((R)-8-Fluorocroman-4-il)-

2-(1*H*-imidazo[4,5-c]piridin-1-il)-5-nitropirimidin-4-amina eluyó en segundo lugar: (1*H*-NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 9.2 (s, 1H), 9.1 (s, 1H), 8.9 (d, 1H), 8.6 (d, 1H), 8.4 (d, 1H), 7.1 (m, 2H), 6.9 (m, 1H), 5.7 (q, 1H), 4.5 (m, 1H), 4.4 (m, 1H), 2.6 (m, 1H), 2.4 (m, 1H).).

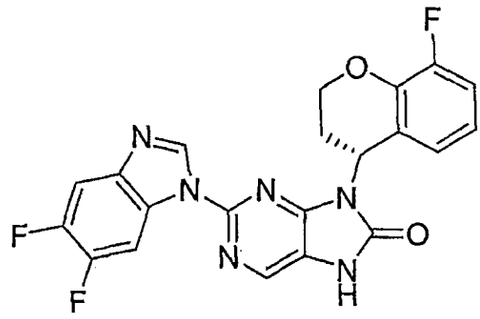


[00227] 9-((R)-8-Fluorocroman-4-il)-2-(3H-imidazo[4,5-c]piridin-3-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de N-((R)-8-fluorocroman-4-il)-2-(3H-imidazo[4,5-c]piridin-3-il)-5-nitropirimidin-4-amina mediante los procedimientos descritos en Ejemplo 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H), 9.4 (s, 1H), 8.6 (d, 1H), 8.3 (m, 2H), 7.0 (t, 1H), 6.7 (m, 2H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (m, 1H).



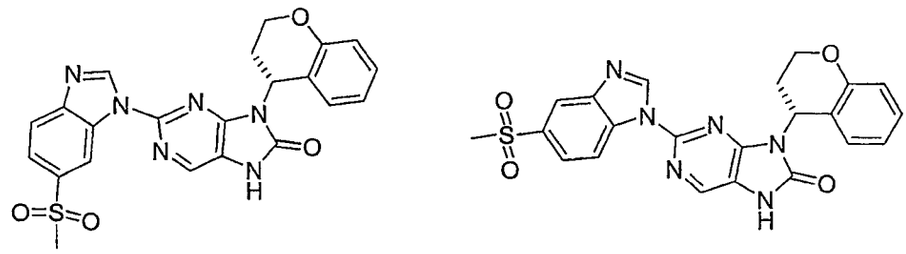
[00228] 9-((R)-8-Fluorocroman-4-il)-2-(1*H*-imidazo[4,5-c]piridin-1-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de N-((R)-8-fluorocroman-4-il)-2-(1*H*-imidazo[4,5-c]piridin-1-il)-5-nitropirimidin-4-amina mediante los procedimientos descritos en Ejemplo 24. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.3 (d, 2H), 8.4 (d, 1H), 8.3 (d, 2H), 7.0 (t, 1H), 6.7 (m, 2H), 5.9 (t, 1H)$_3$ 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (m, 1H).

[00229] Síntesis de 2-(5,6-Difluoro-1H-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona.



[00230] El compuesto del título se sintetizó de 5,6-difluoro-1H-benzo[*d*]imidazol (Ejemplo 4) mediante el procedimiento descrito en Ejemplo 25. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.8 (s, 1H), 8.3 (s, 1H), 7.8 (t, 1H), 7.6 (t, 1H), 7.1 (t, 1H), 6.8 (m, 1H), 5.9 (t, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 3.6 (s, 3H), 2.9 (m, 1H), 2.4 (m, 1H) ppm.

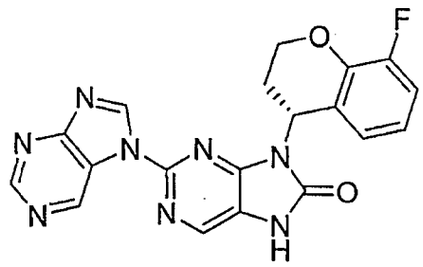
[00231] Síntesis de 9-(*R*)-Croman-4-il-2-(6-metanosulfonil-benzoimidazol-1-il)-7,9-dihidro-purin-8-ona y 9-(*R*)-Croman-4-il-2-(5-metanosulfonil-benzoimidazol-1-il)-7,9-dihidro-purin-8-ona.



[00232] Los compuestos del título se sintetizaron de 5-metilsulfonilbenzimidazol (preparado según los Ejemplos 4 y 5) mediante el procedimiento descrito en Ejemplo 25. Purificación por cromatografía en columna (2% MeOH / DCM) proporcionó 9-(*R*)-croman-4-il-2-(6-metanosulfonil-benzoimidazol-1-il)-7,9-dihidro-purin-8-ona como el primer isómero eluyente: ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.8 (s, 1H), 8.3 (s, 1H), 7.9 (d, 2H), 7.2 (t, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (t, 1H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (t, 1H), 3.1 (s, 3H), 2.9 (m, 1H), 2.4 (m, 1H) ppm, y 9-(*R*)-Croman-4-il-2-(5-metanosulfonil-benzoimidazol-1-il)-7,9-dihidro-purin-8-ona como el segundo isómero eluyente: ^{1}H-NMR ($CDCl_3$) δ 8.9 (s, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 7.8 (d, 1H), 7.2 (m, 1H), 7.1 (d, 1H), 6.9 (d,

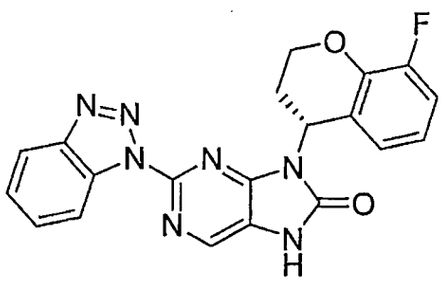
1H), 6.8 (t, 1H), 5.9 (t, 1H), 4.5 (m, 1H), 4.4 (t, 1H), 3.1 (s, 3H), 2.9 (m, 1H), 2.4 (m, 1H) ppm.

[00233] Síntesis de 9-((*R*)-8-Fluorocroman-4-il)-2-(7*H*-purin-7-il)-7*H*-purin-8(9*H*)-ona.



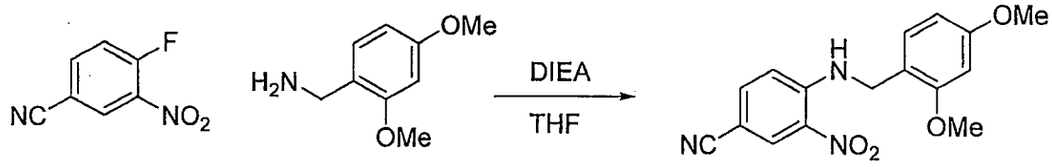
[00234] El compuesto del título se sintetizó de 7*H*-purina mediante el procedimiento descrito en Ejemplo 25. ^{1}H-NMR ($CDCl_3$) δ 9.4 (s, 1H), 9.2 (s, 1H), 9.1 (s, 1H), 8.3 (s, 1H), 7.8 (s, 1H), 7.0 (m, 1H), 6.8 (d, 2H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.9 (m, 1H), 2.4 (m, 1H) ppm.

[00235] Síntesis de 2-(1*H*-Benzo[*d*][1,2,3]triazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona.

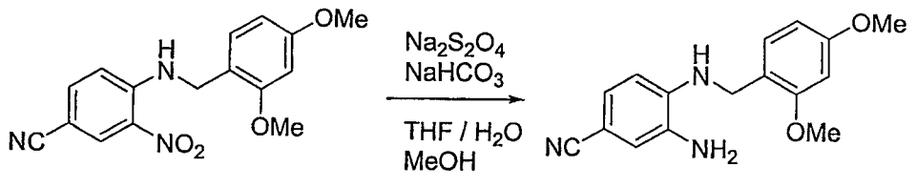


[00236] El compuesto del título se sintetizó de 1*H*-benzo[*d*][1,2,3]triazol mediante el procedimiento descrito en Ejemplo 25. ^{1}H-NMR (5% CD_3OD in $CDCl_3$) δ 8.4 (br s, 1H), 8.0 (d, 1H), 7.5-7.3 (m, 3H), 7.0-6.9 (m, 1H), 6.7 (m, 2H), 5.9 (dd, 1H), 4.5 (dt, 1H), 4.3 (td, 1H), 2.9-2.8 (m, 1H), 2.4-2.2 (m, 1H) ppm.

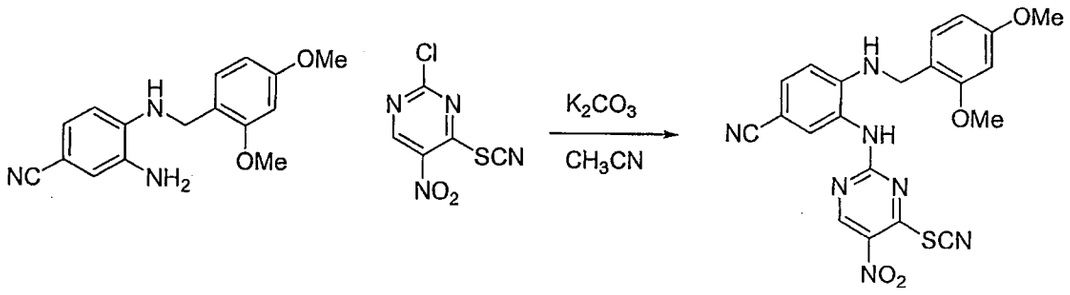
[00237] Ejemplo 26. Síntesis de 3-(9-((*R*)-6,8-difluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo:



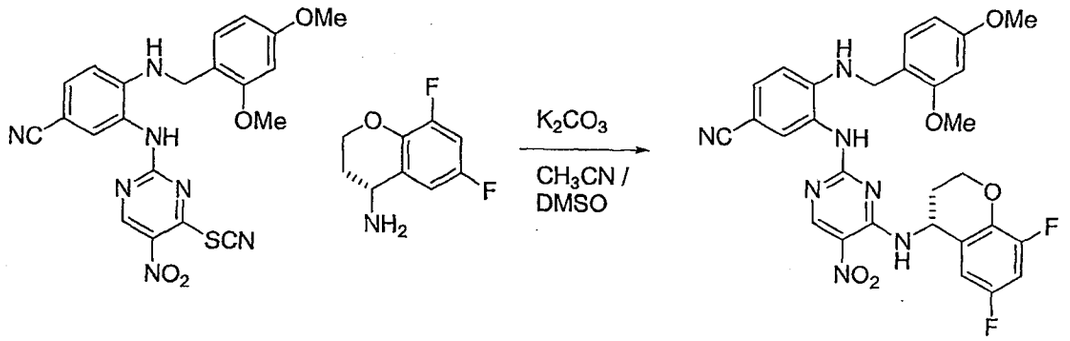
[00238] 4-(2,4-Dimetoxibencilamino)-3-nitrobenzonitrilo. Una solución de 4-fluoro-3-nitrobenzonitrilo (5.0 g) en THF (100 mL) se trató con DIEA (6.3 mL) y 2,4-dimetoxibencilamina (5.0 mL), y luego se agitó durante 24 horas. El disolvente se evaporó y la mezcla cruda se disolvió en EtOAc (100 mL). La solución se lavó una vez con 1 M HCl y dos veces con NaCl acuoso saturado (cada 100 mL). La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. Cromatografía en columna (20% EtOAc / DCM) proporcionó 9.25 g del compuesto del título.



[00239] 4-(2,4-Dimetoxibencilamino)-3-aminobenzonitrilo. Una solución de 4-(2,4-dimetoxibencilamino)-3-nitrobenzonitrilo (4.54 g) en THF (400 mL) se trató con una solución de hidrosulfito de sodio (20 g) y bicarbonato de sodio (10 g) en agua destilada (350 mL). Inmediatamente se agregó suficiente metanol (50 mL) para mantener una solución homogénea. Luego de 15 minutos, se agregaron EtOAc (500 mL) y NaCl acuoso saturado (500 mL) y la capa orgánica se separó. La capa acuosa se extrajo de nuevo con 400 mL de EtOAc. Las capas orgánicas combinadas se lavaron con NaCl acuoso saturado (500 mL) y se separaron. La fase orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo* para proporcionar 4.33 g del compuesto del título.

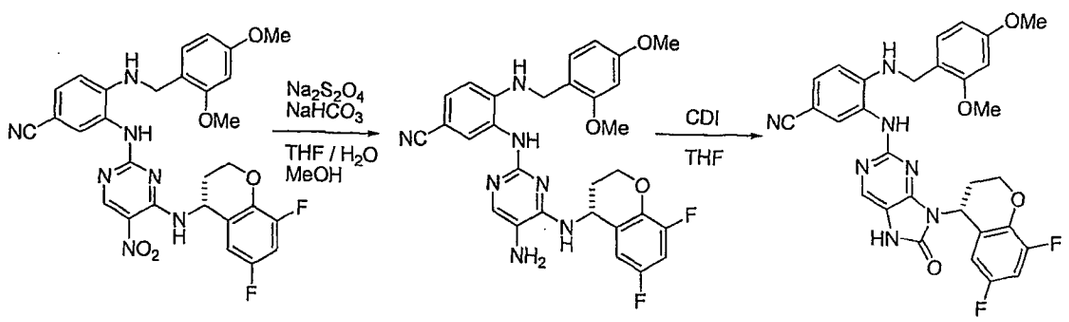


[00240] 4-(2,4-Dimetoxibencilamino)-3-(5-nitro-4-tiocianatopirimidin-2-ilamino)benzonitrilo. Una solución de 4-(2,4-dimetoxibencilamino)-3-aminobenzonitrilo (3.9 g) en acetonitrilo (100 mL) se enfrió a 0 °C y se trató con carbonato de potasio (6.3 g), seguido por una solución que contenía 3 g de 2-cloro-5-nitro-4-tiocianatopirimidina (WO 2003/032994) en acetonitrilo (50 mL). La mezcla se agitó durante 30 minutos a 0 °C y 30 minutos a temperatura de la sala, resultante en la formación de un precipitado. La mezcla se extinguió a 0 °C mediante la adición de 4% ácido acético (150 mL) y se filtró. El precipitado se agitó en 100 mL de acetonitrilo y se filtró otra vez. El precipitado se lavó con acetonitrilo, lo cual resultó en la lenta disolución del producto en el filtrado. Luego de secar con aire, 1.5 g del compuesto del título permanecieron como la torta del precipitado. El filtrado se extrajo con EtOAc, se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. Cromatografía en columna (0→20% EtOAc / DCM) y recristalización de acetonitrilo proporcionó 0.415 g adicionales del compuesto del título.

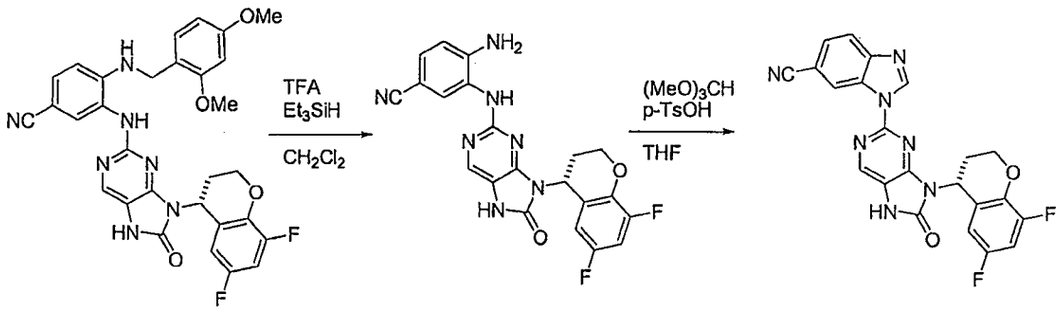


[00241] (R)-4-(2,4-Dimetoxibencilamino)-3-(4-(6,8-difluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino)benzonitrilo. Una suspensión parcial de 4-(2,4-dimetoxibencilamino)-3-(5-nitro-4-tiocianatopirimidin-2-ilamino)benzonitrilo (415 mg) en 40 mL de acetonitrilo se trató con una

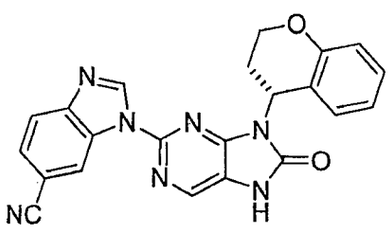
solución de sal HCl de (R)-6,8-difluorocroman-4-amina (320 mg) en DMSO (10 mL), seguida por carbonato de potasio (1.0 g). La mezcla se agitó durante 24 horas, y luego se diluyó con EtOAc (200 mL). La mezcla se lavó una vez con cloruro de amonio acuoso saturado (200 mL) y 3 veces con NaCl acuoso saturado (200 mL cada una). La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. Cromatografía en columna (20→40% EtOAc / hexanos) proporcionó 358 mg del compuesto del título.



[00242] (R)-4-(2,4-Dimetoxibencilamino)-3-(9-(6,8-difluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-ilamino)benzonitrilo. Una solución de (R)-4-(2,4-dimetoxibencilamino)-3-(4-(6,8-difluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino)benzonitrilo (358 mg) en THF (25 mL) se trató con una solución de hidrosulfito de sodio (1.5 g) y bicarbonato de sodio (1.5 g) en 20 mL de agua destilada. Se agregó metanol (5 mL) para mantener una solución homogénea. Después de 15 minutos, la mezcla se diluyó con EtOAc (100 mL) y se lavó con NaCl acuoso saturado (2 X 100 mL). La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo* para proporcionar el intermedio (R)-4-(2,4-dimetoxibencilamino)-3-(5-amino-4-(6,8-difluorocroman-4-ilamino) pirimidin-2-ilamino)benzonitrilo. El intermedio se disolvió en THF (5 mL) y se trató con carbonildiimidazol (0.55 g) durante 16 horas. La mezcla se diluyó con EtOAc (100 mL) y se lavó dos veces con NaCl acuoso saturado (2 X 100 mL). La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. Cromatografía en columna (2-→3% MeOH / DCM) proporcionó 230 mg del compuesto del título.

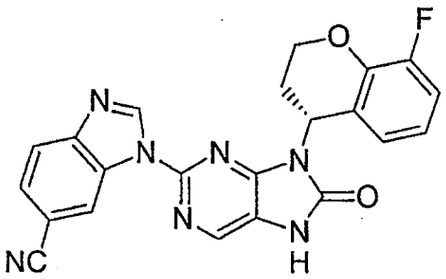


[00243] 3-(9-((R)-6,8-Difluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo. Una solución de (R)-4-(2,4-dimetoxibencilamino)-3-(9-(6,8-difluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-ilamino)benzonitrilo (230 mg) en DCM (5 mL) se trató con TFA (5 mL) y trietilsilano (1 mL) durante 16 horas. La mezcla se concentró *in vacuo* para proporcionar el intermedio (R)-4-amino-3-(9-(6,8-difluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-ilamino)benzonitrilo. El intermedio se disolvió en 5 mL THF y se trató con 3 mL trimetilortoformiato, seguido por ácido p-toluenosulfónico (3 mg). Luego de 1 hora, la mezcla se diluyó con EtOAc (100 mL) y se lavó una vez con bicarbonato de sodio acuoso saturado (100 mL). La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. Cromatografía en columna (50→100% EtOAc / hexanos) proporcionó 78 mg del compuesto del título. ^{1}H-NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 8.8 (s, 1H), 8.7 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.6 (dd, 1H), 6.8 (td, 1H), 6.4 (dd, 1H), 5.8 (dd, 1H), 4.6 (m, 1H), 4.4 (td, 1H), 2.9 (m, 1H), 2.3 (m, 1H).

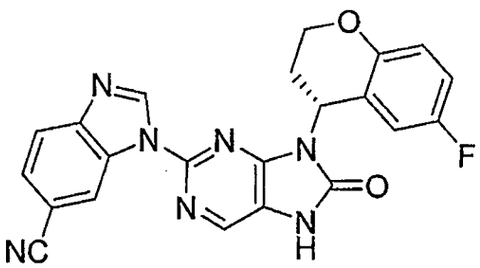


[00244] 3-(9-((R)-Croman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo. El compuesto del título se sintetizó de (*R*)-croman-4-amina mediante los procedimientos descritos en Ejemplo 26. ^{1}H-NMR (300 MHz, 5% CD_3OD en $CDCl_3$) δ 8.8 (s, 1H), 8.5 (s, 1H), 8.2

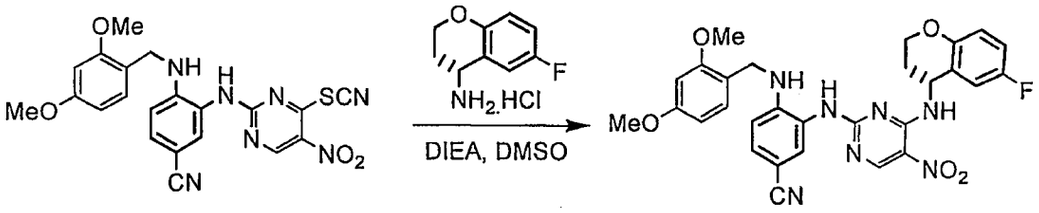
(s, 1H), 7.8 (d, 1H), 7.5 (dd, 1H), 7.1 (m, 2H), 6.8 (d, 1H), 6.7 (td, 1H), 5.8 (dd, 1H), 4.5 (m, 1H), 4.3 (td, 1H), 2.8 (m, 1H), 2.3 (m, 1H).



[00245] 3-[9-(8-Fluoro-croman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il]-3H-benzoimidazol-5-carbonitrilo. El compuesto del título se sintetizó de (*R*)-8-fluorocroman-4-amina mediante los procedimientos descritos en Ejemplo 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.8 (s, 1H), 8.6 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.0 (t, 1H), 6.6 (m, 2H), 5.8 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (m, 1H).

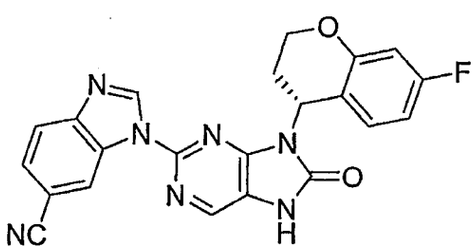


[00246] 3-(9-((R)-6-Fluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo. El compuesto del título se sintetizó de (R)-6-fluorocroman-4-amina mediante los procedimientos descritos en Ejemplo 26. ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.86 (s, 1H), 8.41 (s, 1H), 8.18 (s, 1H), 7.72 (d, 1H), 7.51 (d, 1H), 7.0-7.1 (m, 1H), 6.8-6.9 (m, 1H), 6.49 (dd, 1H), 5.76 (br t, 1H), 4.4-4.5 (m, 1H), 4.24 (br t, 1H), 2.7-2.9 (m, 1H), 2.2-2.3 (m, 1H). Las condiciones para la introducción de la cromanil amina se mejoraron como se describe a continuación:



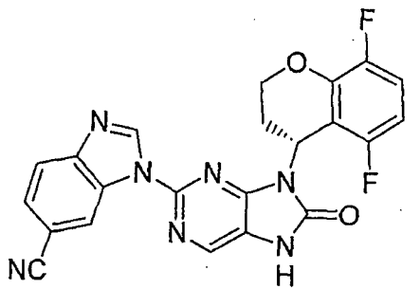
[00247] **(*R*)-4-(2,4-Dimetoxibencilamino)-3-(4-(6-fluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino)benzonitrilo**. Una solución de 4-(2,4-dimetoxibencilamino)-3-(5-nitro-4-tiocianatopirimidin-2-ilamino)benzonitrilo (139 mg) en DMSO anhidro (3 mL) se agregó a una solución de clorhidrato de (*R*)-6-fluorocroman-4-amina (79 mg) en DMSO anhidro (3 mL) y DIEA (0.21 mL). La solución rojo oscuro resultante se agitó a temperatura de la sala bajo una atmósfera de Ar, tiempo durante el cual la solución se aclara a amarillo. Una vez concluida la reacción, la mezcla se enfrió a 0 °C con un baño helado, y se agregó agua (25 mL) (exoterma). El sólido amarillo resultante se recogió mediante filtración, se lavó con más agua, se secó con aire, luego se disolvió en CH_2Cl_2, se secó la solución orgánica ($MgSO_4$), se filtró y se evaporó para proporcionar el compuesto del título (cuant.), NMR $CDCl_3$ ^1H δ 9.0 (s, 1H), 8.6 (d, 1H), 7.7 (br s, 1H), 7.4 (dd, 1H), 7.1 (d, 1H), 7.0-6.8 (m, 4H), 6.5-6.4 (m, 2H), 5.2 (br s, 1H), 4.3 (s, 2H), 4.2 (br s, 2H), 3.8 (s, 6H), 2.2 (br s, 1H), 1.8 (br s, 1H); ^{19}F δ -123 ppm; $MH^+ = 572$.

[00248] Este material se obtuvo usando los mismos procedimientos descritos en Ejemplo 26 para producir 3-(9-((*R*)-6-fluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3*H*-benzo[*d*]imidazol-5-carbonitrilo.



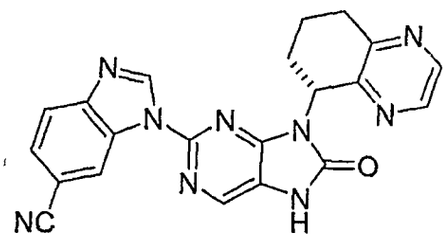
[00249] **3-(9-((R)-7-Fluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo**. El compuesto del título se

sintetizó de (R)-7-fluorocroman-4-amina mediante los procedimientos descritos en Ejemplo 26. ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.86 (s, 1H), 8.58 (s, 1H), 8.19 (s, 1H), 7.79 (d, 1H), 7.56 (d, 1H), 6.7-6.9 (m, 2H), 6.4-6.5 (m, 1H), 5.78 (br t, 1H), 4.5-4.6 (m, 1H), 4.32 (br t, 1H), 2.7-2.9 (m, 1H), 2.2-2.4 (m, 1H).



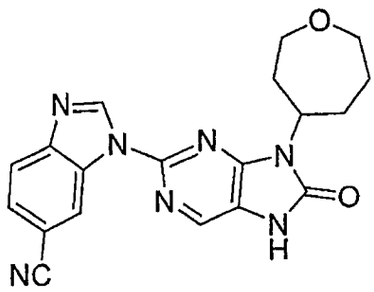
[00250] 3-[9-(5,8-Difluoro-croman-4-il)-8-oxo-8,9-dihidro-7H-purin-2-il]-3H-benzoimidazol-5-carbonitrilo. El compuesto del título se sintetizó de (*R*)-5,8-difluorocroman-4-amina mediante los procedimientos descritos en Ejemplo 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.8 (s, 1H), 8.7 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.0 (m, 1H), 6.4 (m, 1H), 5.9 (t, 1H), 4.6 (m, 1H), 4.4(m, 1H), 2.5(m, 2H).

[00251] Síntesis de 3-(8-Oxo-9-((*R*)-5,6,7,8-tetrahidroquinoxalin-5-il)-8,9-dihidro-7*H*-purin-2-il)-3*H*-benzo[*d*]imidazol-5-carbonitrilo.



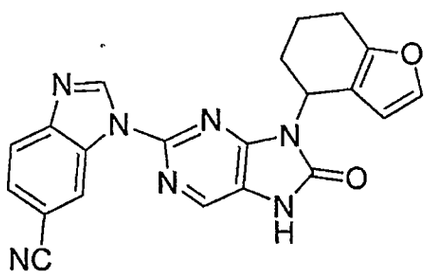
[00252] El compuesto del título se sintetizó de (*R*)-5,6,7,8-tetrahidroquinoxalin-5-amina (Ejemplo 34) mediante el procedimiento descrito en Ejemplo 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.8 (br, 1H), 8.9 (s, 1H), 8.6 (s, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.6 (d, 2H), 5.9 (dd, 2H), 3.2-3.5 (m, 2H), 2.8 (q, 1H), 2.3-2.5 (m, 2H), 2.1 (m, 1H).

[00253] Síntesis de 3-(9-Oxepan-4-il-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzoimidazol-5-carbonitrilo.



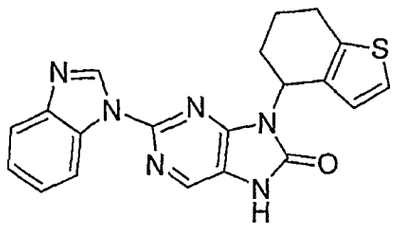
[00254] El compuesto del título se sintetizó de oxepan-4-amina (obtenida de oxepan-4-ona (Chemische Berichte, 1958, *91*, 1589) mediante reducción de oxime de acuerdo con el Ejemplo 29) mediante el procedimiento descrito en Ejemplo 26. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s, 1H), 9.0 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.6 (d, 1H), 4.7 (t, 1H), 3.8 (m, 6H), 2.7 (m, 2H), 2.0 (m, 2H) ppm.

[00255] Síntesis de 3-(8-Oxo-9-(4,5,6,7-tetrahidrobenzofuran-4-il)-8,9-dihidro-7H-purin-2-il)-3*H*-benzo[*d*]imidazol-5-carbonitrilo.



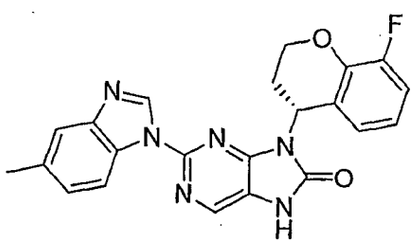
[00256] El compuesto del título se sintetizó de 4,5,6,7-tetrahidrobenzofuran-4-amina (obtenida mediante aminación reductora de 6,7-dihidrobenzofuran-4(5H)-ona según Ejemplo 33) mediante el procedimiento descrito en Ejemplo 26 ^{1}H-NMR ($CDCl_3$) δ 9.0 (s, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.6 (d, 1H), 7.3 (s, 1H), 6.0 (s, 1H), 5.6 (t, 1H), 3.0 (m, 1H), 2.8 (d, 2H), 2.3 (m, 3H), 2.0 (m, 1H) ppm.

[00257] Síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(4,5,6,7-tetrahidrobenzo[*b*]tiofen-4-il)-7*H*-purin-8(9*H*)-ona.



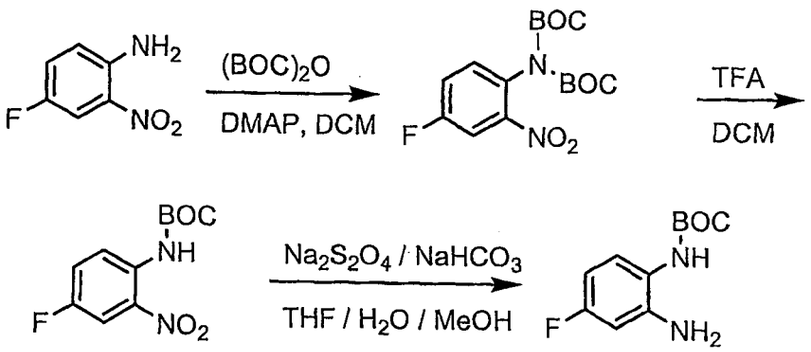
[00258] El compuesto del título se sintetizó de 4,5,6,7-tetrahidrobenzo[*b*]tiofen-4-amina (obtenida por aminación reductora de 6,7-dihidrobenzo[*b*]tiofen-4(5*H*)-on según Ejemplo 33) mediante el procedimiento descrito en Ejemplo 26 ^{1}H-NMR (5% CD_3OD in $CDCl_3$) δ 9.2 (s, 1H), 8.2 (s, 1H), 7.8-7.7 (m, 2H), 7.4 (m, 2H), 7.0 (d, 1H), 6.6 (d, 1H), 5.7 (dd, 1H), 3.0 (br s, 2H), 2.4-2.0 (m, 4H) ppm.

[00259] Síntesis de 9-((*R*)-8-Fluorocroman-4-il)-2-(5-metil-1*H*-benzo[*d*]imidazol-1-il)-7*H*-purin-8(9*H*)-ona.



[00260] El compuesto del título se sintetizó de (*R*)-8-fluorocroman-4-amina y 4-fluoro-3-nitrotolueno mediante los procedimientos descritos en Ejemplo 26. ^{1}H-NMR ($CDCl_3$) δ 9.0 (s, 1H), 8.2 (s, 1H), 7.6 (d, 1H), 7.5 (s, 1H), 7.1 (d, 1H), 6.9 (m, 2H), 5.8 (t, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 2.8 (m, 1H), 2.4 (s, 3H), 2.3 (m, 1H) ppm.

[00261] Ejemplo 27. Síntesis de 2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluoro-croman-4-il)-7*H*-purin-8(9*H*)-ona:

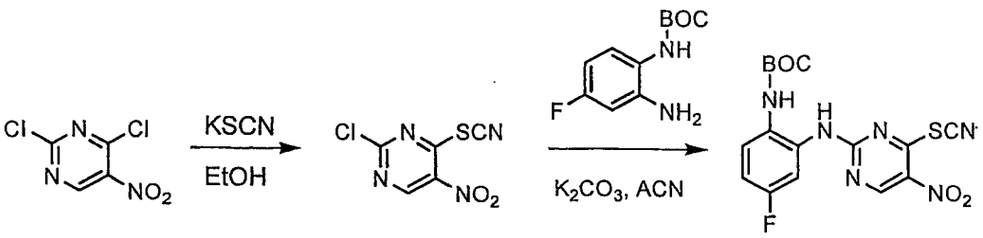


[00262] 4-Fluoro-2-nitro-fenil di-*terc*-butil imidodicarbonato. Una cantidad catalítica de DMAP se agregó a una mezcla de 4-fluoro-2-nitrobencenamina (0.78 g) y di-*terc*-butil dicarbonato (2.18 g) en DCM (20 mL) y se agitó a temperatura de la sala durante 15 horas. La mezcla se diluyó con H_2O y se extrajo dos veces con DCM. Los orgánicos combinados se secaron, se filtraron y se evaporaron para proporcionar el material bis-BOC (cuant.). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.8 (dd, 1H), 7.3 (m, 2H), 1.4 (s, 18H).

[00263] *terc*-Butil 4-fluoro-2-nitrofenilcarbamato. (Procedimiento: Connell, R. D.; Rein, T.; Akermark, B.; Helquist, P. J. *J. Org. Chem.* 1988, *53*, 3845). A una solución agitada del material Bis-BOC en DCM (20 mL) se agregó TFA (0.58 mL). Luego de 3 horas la reacción se extinguió con $NaHCO_3$ acuoso (5 mL), se agregó salmuera, la mezcla se separó y se extrajo con más DCM. Los orgánicos combinados se evaporaron, se purificaron mediante cromatografía en columna (eluida con 7.5% EtOAc/Hex) para proporcionar el producto del título (1.12 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.5 (br IH), 8.5 (dd, 1H), 7.9 (dd, 1H), 7.3 (m, 1H), 1.5 (s, 9H).

[00264] *terc*-Butil 2-amino-4-fluorofenilcarbamato. A una solución de *terc*-butil 4-fluoro-2-nitrofenilcarbamato (0.34 g) en THF (30 mL) se agregó una solución pre-mezclada de hidrosulfito de sodio (2 g) y bicarbonato de sodio (1g) en agua (50 mL). Se agregó también MeOH (10 mL) para contribuir a la solución de la mezcla, la cual se agitó a

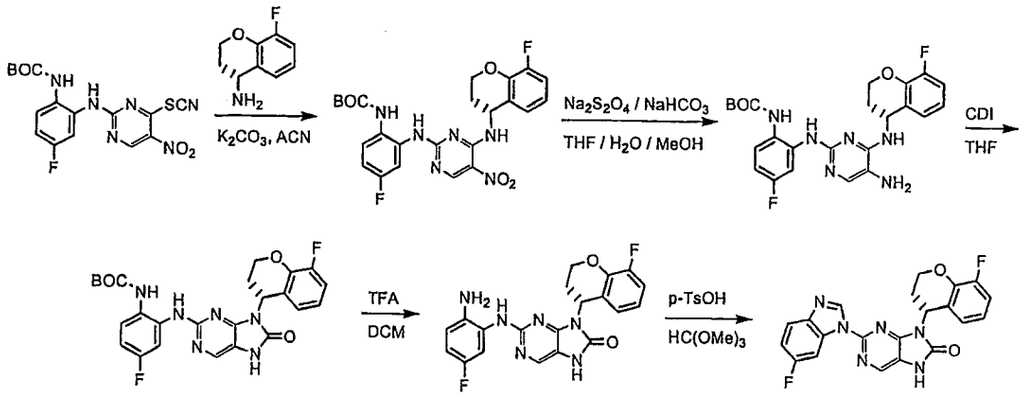
temperatura de la sala durante 30 minutos, cuando se agregó cloruro de sodio para saturar la solución. La mezcla resultante se extrajo con EtOAc (2x). Los orgánicos combinados se secaron, se filtraron y se evaporaron para proporcionar el compuesto del título (cuant.), que se utilizó como tal para el siguiente paso. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.5 (dd, 1H), 6.6 (dd, 1H), 6.5 (m, 1H), 6.4 (br IH), 4.7 (br 2H), 1.5 (s, 9H); MH^+ = 227 (menor) 127 (-BOC), 171 (-*t*Bu).



[00265] 2-Cloro-5-nitro-4-tiocianatopirimidina. (Compuesto conocido, por ejemplo, WO 2003/032994). Tiocianato de potasio (0.97 g, 10 mM) se agregó a una solución de 2,4-dicloro-5-nitropirimidina (1.94 g 10, mM) en EtOH (40 mL) enfriada a 0 °C mediante un baño helado. La solución se agitó a 0 °C durante 30 minutos, luego se retiró el baño y la suspensión resultante se dejó alcanzar la temperatura de la sala durante 60 minutos, cuando se agregó agua (100 mL). El precipitado se recogió mediante filtración, se lavó con agua helada, se disolvió con DCM, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el compuesto del título (1.7 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H).

[00266] *terc*-Butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino) fenilcarbamato. Carbonato de potasio (207 mg) se agregó a una solución agitada de 2-cloro-5-nitro-4-tiocianatopirimidina (108 mg) y *terc*-butil 4-fluoro-2-nitrofenilcarbamato (113 mg) en ACN (5 mL) y se agitó durante 15 horas. La solución se diluyó con salmuera y se extrajo con EtOAc (2x). Los orgánicos combinados se evaporaron y se purificaron mediante cromatografía en columna; la elución con 30 % EtO Ac/Hex produjo el compuesto del título (144 mg, 71 % de rendimiento). ^{1}H-NMR (300 MHz,

DMSO-d6) δ 10.5 (br s, 1H), 9.3 (br s, 1H), 8.9 (br s, 1H), 7.7-7.4 (m, 2H), 7.1 (br s, 1H), 1.5 (s, 9H), 1.5 (s, 9H); MH^+ = 407, 307 (-BOC), 351 (-*t*Bu).



[00267] (*R*)-*terc*-Butil 4-fluoro-2-(4-(8-fluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino)fenilcarbamato. Una solución del clorhidrato de (*R*)-8-fluorocroman-4-amina (104 mg) en DMSO (2 mL) y carbonato de potasio (141 mg) se agregaron a una solución agitada de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato (140 mg) en ACN (10 mL). La mezcla se agitó durante 15 horas a temperatura de la sala, luego se repartió en porciones entre salmuera y EtOAc, y se separó. La capa acuosa se lavó con más EtOAc, los orgánicos combinados se evaporaron y se purificaron mediante cromatografía en columna; la elución con 20-30 % EtOAc/H suministró el producto del título en 83 % de rendimiento. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.1 (s, 1H), 8.7 (m, 1H), 8.2 (br s, 1H), 7.7 (m, 1H), 7.3 (m, 1H), 7.3-6.8 (m, 4H), 6.5 (s, 1H), 5.5 (br s, 1H), 4.4 (m 2H), 2.4 (m, 1H), 2.2 (m, 1H), 1.5 (s, 9H); MH^+ = 515, 459 (-*t*Bu).

[00268] (*R*)-*terc*-Butil 4-fluoro-2-(9-(8-fluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-ilamino)fenilcarbamato. A una solución de (*R*)-*terc*-butil 4-fluoro-2-(4-(8-fluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino) fenilcarbamato (141 mg) en THF (20 mL) se agregó una solución pre-mezclada de hidrosulfito de sodio (0.6 g) y bicarbonato de sodio (0.3g) en agua (50 mL). Se agregó también MeOH (5 mL) para contribuir a la solución de la mezcla, la cual se agitó a temperatura de la sala durante 30 minutos, cuando se agregó cloruro de sodio para saturar la solución. La mezcla resultante se extrajo con EtOAc (2x), los orgánicos combinados se

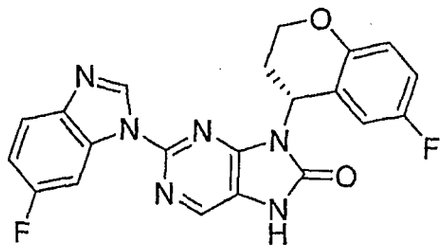
secaron, se filtraron y se evaporaron para proporcionar (*R*)-*terc*-butil 2-(5-amino-4-(8-fluorocroman-4-ilamino)pirimidin-2-ilamino)-4-fluorofenilcarbamato, que se utilizó como tal para el siguiente paso, MH^+ = 485.

[00269] A una solución agitada del material anterior en THF (5 mL) se agregó CDI (131 mg). Luego de 15 horas, se agregaron salmuera y EtOAc, y la mezcla se separó. La capa acuosa se lavó con más EtOAc y los orgánicos combinados se evaporaron y se purificaron mediante cromatografía en columna (eluida con3 % MeOH/DCM) para proporcionar el producto del título (86 mg, 62 % de rendimiento para dos pasos). ^{1}H-NMR (300 MHz, 5% CD_3OD in $CDCl_3$) δ 7.9 (s, 1H), 7.4 (dd, 1H), 7.3 (m, 1H), 6.9 (dd, 1H), 6.7-6.5 (m, 3H), 5.7 (dd, 1H), 4.6 (m, 1H), 4.3(td, 1H), 2.9 (m, 1H), 2.2 (m, 1H), 1.5 (s, 9H); MH^+ = 511, 411 (-BOC), 455 (-*t*Bu).

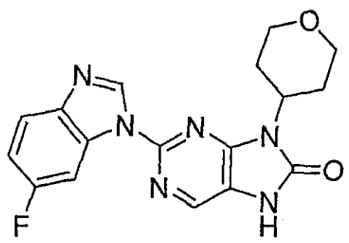
[00270] 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*- purin-8(9*H*)-ona. Una solución recién preparada de 30 % TFA/DCM (5 mL) se agregó a (*R*)-*terc*-butil 4-fluoro-2-(9-(8-fluorocroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-ilamino)fenilcarbamato, y la solución se agitó a temperatura de la sala durante 60 minutos, luego se retiraron los disolventes *in vacuo* para proporcionar (*R*)-2-(2-amino-5-fluorofenilamino)-9-(8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona, que se utilizó tal como estaba. MH^+

[00271] A la di-amina anterior se agregó MeOH (2 mL), trimetilortoformiato (2 mL) y *p*-TsOH (cat). La mezcla se agitó a temperatura de la sala durante 60 minutos; en seguida los disolventes se redujeron y el material resultante se repartió en porciones entre DCM y salmuera, y se separó. El producto crudo se purificó mediante cromatografía en columna (eluida con 4 % MeOH/DCM) para proporcionar el compuesto del título (46 mg). ^{1}H-NMR (300 MHz, 5% CD_3OD en

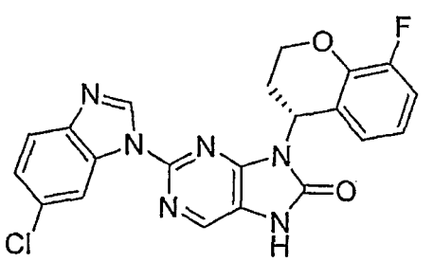
$CDCl_3$) δ 8.7 (s, 1H), 8.1 (s, 1H), 7.5 (m, 2H), 6.9 (m, 2H), 6.6 (m, 2H), 5.8 (dd, 1H), 4.6 (m, 1H), 4.3 (td, 1H), 2.8 (m, 1H), 2.3 (m, 1H); $MH^+ = 421$.



[00272] 2-(6-Fluoro-1H-benzo[*d*]imidazol-1-il)-9-((R)-6-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de (*R*)-6-fluorocroman-4-amina mediante los procedimientos descritos en Ejemplo 27. ^{1}H NMR (300 MHz, $CDCl_3$+ 5%CD_3OD): δ 8.72 (s, 1H), 8.16 (s, 1H), 7.5-7.7 (m, 2H), 6.9-7.0 (m, 2H), 6.8-6.9 (m, 1H), 6.54 (dd, 1H), 5.78 (br t, 1H), 4.4-4.5 (m, 1H), 4.26 (m, 1H), 2.7-2.8 (m, 1H), 2.2-2.3 (m, 1H).



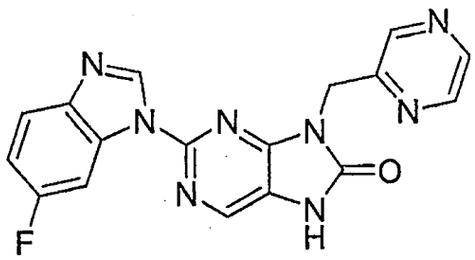
[00273] 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(tetraliydro-2H-piran-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de 4-aminotetrahidropiran mediante los procedimientos descritos en Ejemplo 27. ^{1}H NMR (d_6-DMSO) δ 11.65 (s, 1H), 9.13 (s, 1H), 8.34 (s, 1H), 8.28 (m, 1H), 7.82 (m, 1H), 7.25 (td, J = 9.0, 2.4 Hz, 1H), 4.56 (m, 1H), 4.03 (dd, J = 11.1, 3.9 Hz, 2H), 3.50 (t, J = 11.1 Hz, 2H), 2.59 (m, 2H), 1.78 (m, 2H).



[00274] 2-(6-Cloro-1*H*-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de (*R*)-8-fluorocroman-4-amina y 4-cloro-2-nitrobencenamina mediante los

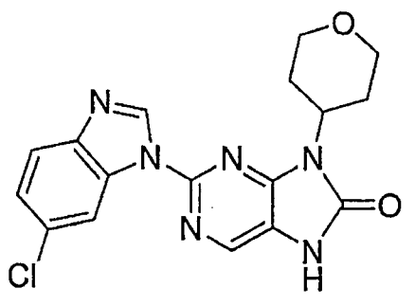
procedimientos descritos en Ejemplo 27. ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 8.7 (s, 1H), 8.2 (s, 1H), 8.1 (s, 1H), 7.6 (d, 1H), 7.2 (dd, 1H), 6.9 (td, 1H), 6.7-6.5 (m, 2H). 5.8 (dd, 1H), 4.6 (m, 1H), 4.4 (td, 1H), 2.9 (m, 1H), 2.3 (m, 1H).

[00275] Síntesis de 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-(pirazin-2-ilmetil)-7*H*-purin-8(9*H*)-ona.



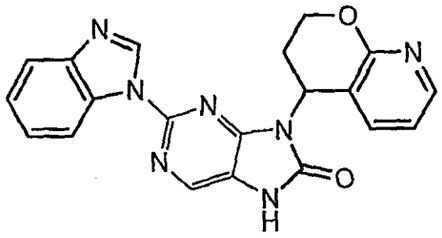
[00276] El compuesto del título se sintetizó de pirazin-2-ilmetanamina mediante el procedimiento descrito en Ejemplo 27. ^{1}H-NMR (300 MHz, $CDCl_3$ + 5% CD_3OD) δ 8.9 (br, 1H), 8.7 (s, 1H), 8.5 (s, 1H), 8.5 (s, 1H) 8.2 (s, 1H), 8.2(dd, 1H), 7.7 (dd, 1H), 7.0 (td, 1H), 5.3 (s, 2H).

[00277] Síntesis de 2-(6-Cloro-1*H*-benzo[*d*]imidazol-1-il)-9-(tetrahidro-2H-piran-4-il)-7*H*-purin-8(9*H*)-ona.

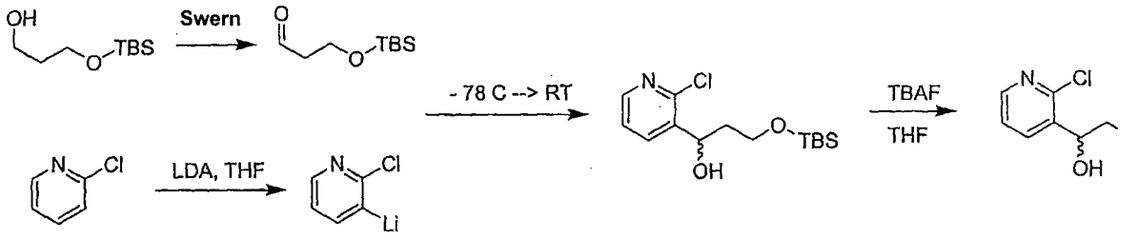


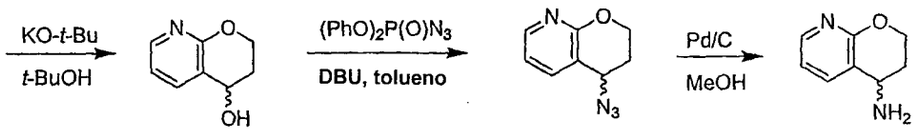
[00278] El compuesto del título se sintetizó de 4-aminotetrahidropirano y 4-cloro-2-nitrobencenamina mediante los procedimientos descritos en Ejemplo 27 ^{1}H NMR (CD_3OD + $CHCl_3$) δ 9.15 (s, 1H), 8.67 (d, 1H), 8.27 (s, 1H), 7.70 (d, 1H), 7.37 (dd, 1H), 4.64 (m, 1H), 4.18 (m, 2H), 3.61 (m, 2H), 2.81 (m, 2H), 1.85 (m, 2H); MS (MH^+) 371.1.

[00279] Procedimiento para la síntesis de 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(3,4-dihidro-2H-pirano[2,3-*b*]piridin-4-il)-7*H*-purin-8(9*H*)-ona.



[00280] Síntesis de 3,4-dihidro-2*H*-pirano[2,3-*b*]piridin-4-amina





[00281] **3-(*terc*-Butildimetilsililoxi)-1-(2-cloropiridin-3-il)propan-1-ol.** (Preparado análogamente al procedimiento de la literatura, Murtiashaw, C. W., *et. al. J. Org. Chem.*, 1992, 57, 1930-1933). Una solución de 3-(*terc*-butildimetilsililoxi)propanol (2.3g, preparado de 3-(*terc*-butildimetilsililoxi)propan-1-ol mediante oxidación de Swern según Li, X.; Lantrip, D.; Fuchs, P. L. *J. Am. Chem. Soc*, 2003, *125*, 14262-14263, información de soporte) en THF (10 mL) se agregó lentamente mediante una aguja de dos extremos a una solución de 2-cloro-3-litiopiridina (preparada a su vez de LDA recién preparado (11.4 mM) y 2-cloropiridina (11.4 mM) (según Gribble, G. W.; Saulnier, M. G. *Tet. Lett.* 1980, 21, 4137-4140) en THF (25 mL) a -78 °C. La mezcla resultante se dejó calentar lentamente a temperatura de la sala durante 15 horas, se extinguió mediante la adición de NH_4Cl saturado (2 mL), y los disolventes se redujeron *in vacuo*. La suspensión resultante se tomó en EtOAc, se lavó con salmuera, y se purificó mediante cromatografía en columna (eluida con 15, 20 y 25 %

EtO Ac/Hex) para proporcionar el producto del título (1.0 g), NMR $CDCl_3$ ^1H δ 8.3 (dd, 1H), 8.0 (dd, 1H), 7.3 (dd, 1H), 5.2 (d, 1H), 4.5 (m, 1H), 4.0-3.8 (m, 2H), 2.1 (m, 1H), 1.8 (m, 1H) 0.9 (s, 9H), 0.1 (s, 6H); MH^+ = 302/304.

[00282] 1-(2-Cloropiridin-3-il)propano-1,3-diol. Una solución de fluoruro de tetrabutilamonio en THF (1M, 3.3mL) se agregó a una solución de 3-(*terc*-butildimetilsililoxi)-1-(2-cloropiridin-3-il)propan-1-ol en THF (5 mL) y se agitó durante 60 minutos, luego se agregó gel de sílice y los disolventes se retiraron bajo presión reducida. Todo el contenido del matraz se agregó a una columna, que se preparó y se eluyó con 75 % ETOAC/Hex, para proporcionar el producto del título (0.49 g), NMR CD_3OD ^1H δ 8.3 (dd, 1H), 8.0 (dd, 1H), 7.4 (dd, 1H), 5.1 (dd, 1H), 3.8 (m, 2H), 2.0 (m, 1H), 1.8 (m, 1H); MH^+ = 188/190.

[00283] 3,4-Dihidro-2*H*-pirano[2,3-b]piridin-4-ol. *terc*-Butóxido de potasio (0.88 g) se agregó a una solución de 1-(2-cloropiridin-3-il) propano-1,3-diol (0.49g) en *terc*-butanol, y la solución se calentó a reflujo durante 3 horas, se dejó enfriar a temperatura de la sala, se extinguió mediante la adición de NH_4Cl saturado(2 mL); los disolventes se redujeron, luego de agregó gel de sílice, y los disolventes restantes se retiraron *in vacuo*. El material se agregó a una columna de gel de sílice que se eluyó con EtOAc y 1% MeOH/EtOAc para proporcionar el producto del título (0.35 g) NMR $CDCl_3$ ^1H δ 8.1 (dd, 1H), 7.7 (dd, 1H), 6.9 (dd, 1H), 4.9 (dd, 1H), 4.5 (m, 2H), 2.1 (m, 2H); MH^+ = 152.

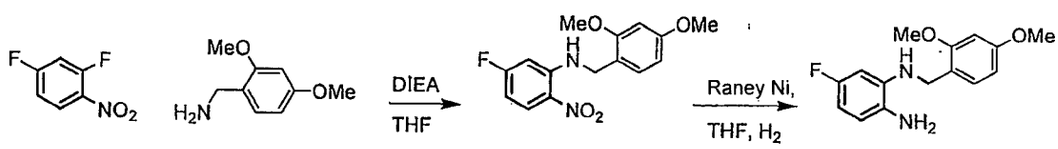
[00284] 4-Azido-3,4-dihidro-2*H*-pirano[2,3-*b*]piridina. (Preparación ref.: Phompson, A. S. *et. al. J. Org. Chem.*, 1993, 58, 5886-5888). Difenil fosforil azida (0.81 mL) se agregó a una suspensión de 3,4-dihidro-2*H*-pirano[2,3-5]piridin-4-ol (0.37 g) en tolueno seco (10 mL), luego la mezcla se enfrió a 0°C bajo una atmósfera de Ar. Se agregó DBU puro (0.56 mL), y la mezcla bifásica resultante se agitó a 0°C durante 2 horas y a

continuación a temperatura de la sala durante 15 horas. La solución bifásica se diluyó con $NaHCO_3$ saturado y se extrajo con DCM (2 x). Los orgánicos combinados se concentraron y se purificaron mediante cromatografía en gel de sílice usando 10, 25 y 50 % de eluyentes EtO Ac/Hex para proporcionar el producto del título (0.31 g) NMR $CDCl_3$ ^1H δ 8.2 (dd, 1H), 7.6 (dd, 1H), 7.0 (dd, 1H), 4.7 (dd, 1H), 4.4 (m, 2H), 2.2 (m, 1H), 2.1 (m, 1H); $MH^+ = 177$.

[00285] **3,4-Dihidro-2*H*-pirano[2,3-*b*]piridin-4-amina**. Una cantidad catalítica de Pd/C (9 mg) se agregó a una solución de 4-azido-3,4-dihidro-2*H*-pirano[2,3-*b*]piridina (88 mg) en MeOH (5 mL). Se cerró el matraz con un tabique, se vació bajo vacío (***"under house vacuum"***), y se agregó hidrógeno a través de un balón. La suspensión resultante se agitó a temperatura de la sala durante 60 minutos, cuando se retiró el balón H_2, se vació la mezcla y se filtró a través de un tapón de celita, que se enjuagó concienzudamente con MeOH. El retiro de los disolventes produjo el compuesto del título (73 mg), NMR $CDCl_3$ ^1H δ 8.1 (dd, 1H), 7.7 (dd, 1H), 6.9 (dd, 1H), 4.5-4.3 (m, 2H), 4.1 (dd, 1H), 2.2 (m, 1H), 1.9 (m, 1H), 1.6 (br s, 2H); $MH^+ = 151$.

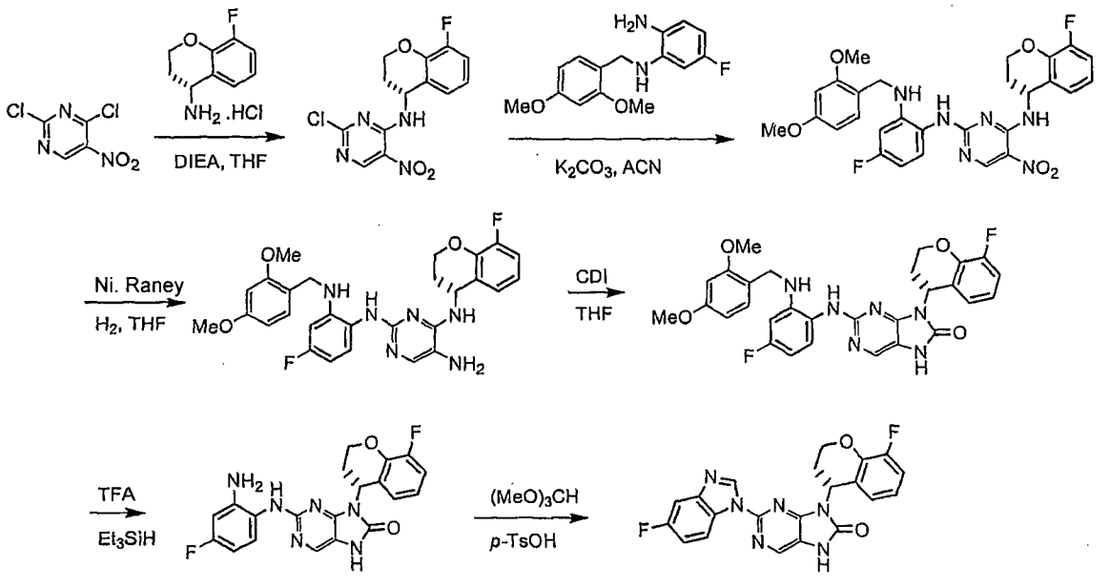
[00286] 2-(1*H*-Benzo[*d*]imidazol-1-il)-9-(3,4-dihidro-2H-pirano[2,3-*b*] piridin-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se preparó en idéntica manera a la descrita en Ejemplo 19 de 3,4-dihidro-2*H*-pirano[2,3-*b*]piridin-4-amina. ^1H NMR ($CDCl_3$ + 5% CD_3OD) δ 8.8 (s, 1H), 8.2 (s, 1H), 8.1 (m, 1H), 7.7 (m, 2H), 7.3 (m, 2H), 6.8 (dd, 2H), 5.9 (dd, 1H), 4.7 (m, 1H), 4.5 (td, 1H), 2.9 (m, 1H), 2.3 (m, 1H); $MH^+ = 386$.

[00287] Ejemplo 28: Síntesis de 2-(5-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona:



[00288] ***N*-(2,4-Dimetoxibencil)-5-fluoro-2-nitrobencenamina**. Una solución de 2,4-difluoro-1-nitrobenceno (1.1 mL), 2,4-dimetoxi bencilamina (1.5 mL) y DIEA (5.2 mL), en THF (40 mL) se calentó a 60 °C durante 60 minutos, se dejó enfriar a temperatura de la sala, se repartió en porciones entre EtOAc y H_2O, se separó, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto del título como un sólido amarillo (3.14 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.5 (br s, 1H), 7.2 (dd, 1H), 7.2 (d, 1H), 6.6-6.4 (m, 3H), 6.3 (m, 1H), 4.3 (d, 2H), 3.9 (s, 3H), 3.8 (s, 3H).

[00289] ***N*^{1}-(2,4-Dimetoxibencil)-5-fluorobenceno-1,2-diamina**. Bajo un chorro de Ar, una cantidad catalítica de una solución de níquel de Raney en agua se agregó a una solución de *N*-(2,4-dimetlioxibencil)-5-fluoro-2-nitrobencenamina (0.5 g) en THF (20 mL). Se cerró el matraz con un tabique, se vació bajo vacío, y se agregó hidrógeno a través de un balón. La suspensión resultante se agitó a temperatura de la sala durante 16 horas, cuando se retiró el balón H_2, se vació la mezcla y se filtró a través de un tapón de celita, que se enjuagó concienzudamente con THF y MeOH, para proporcionar la diamina del título que se usó tal como estaba.



[00290] **(*R*)-2-Cloro-*N*-(8-fluorocroman-4-il)-5-nitropirimidin-4-amina**. Una solución de clorhidrato de (*R*)-8-fluorocroman-4-amina (1.02 g) y DIEA (2.6 mL) en DCM (10 mL) se agregó lentamente a una solución de

2,4-dicloro-5-nitropirimidina (0.97 g) THF (25 mL) a -78 °C. La mezcla de reacción se agitó durante 30 minutos a -78°C, luego se dejó calentar a temperatura de la sala de un día para otro. La reacción se extinguió con la adición de NH_4Cl saturado (1 mL), se redujo el volumen del disolvente *in vacuo*, y la mezcla resultante se repartió en porciones entre EtOAc y agua, luego se separó. El material crudo se purificó mediante cromatografía en columna; la elución con 30 % EtOAc/Hex suministró el producto del título (1.43 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.1 (s, 1H), 8.6 (br d, 1H), 7.1-6.8 (m, 3H), 5.6 (dd, 1H), 4.4 (m, 1H), 4.3(m, 1H), 2.4 (m, 1H), 2.2 (m, 1H).

[00291] **(*R*)-*N*^{2}-(2-(2,4-Dimetoxibencilamino)-4-fluorofenil)-*N*^{4}-(8-fluorocroman-4-il)-5-nitropirimidin-2,4-diamina**. Una mezcla de (*R*)-2-cloro-*N*-(8-fluorocroman-4-il)-5-nitropirimidin-4-amina (32 mg), *N*^{1}-(2,4-dimetoxibencil)-5-fluorobenceno-1,2-diamina (28 mg) y KCO_3 (41 mg) en ACN se calentó a 65 °C durante 3 horas, se enfrió a temperatura de la sala, se diluyó con salmuera y se extrajo con EtOAc (2x). Los orgánicos combinados se evaporaron, y se purificaron mediante cromatografía en columna (eluida con 30 % EtO Ac/Hex) para proporcionar el producto del título (21 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.6 (br d, 1H), 7.2-6.8 (m, 6H), 6.5-6.3 (m,4H), 4.4-4.2 (m, 4H), 3.8 (s, 6H), 2.3-2.2 (m, 2H).

[00292] **(*R*)-2-(2-(2,4-Dimetoxibencilamino)-4-fluorofenilamino)-9-(8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona**. Bajo una atmósfera de Ar, una cantidad catalítica de una solución de níquel de Raney en agua se agregó a una solución de (*R*)-*N*^{2}-(2-(2,4-dimetoxibencilamino)-4-fluorofenil)-*N*^{4}-(8-fluorocroman-4-il)-5-nitropirimidin-2,4-diamina (21 mg) en THF. Se cerró el matraz con un tabique, se vació bajo vacío, y se agregó hidrógeno a través de un balón. La suspensión resultante se agitó a temperatura de la sala durante 2 horas, cuando se retiró el balon H_2, la mezcla se vació y se filtró a través de un tapón de celita, que se enjuagó concienzudamente con THF y MeOH, para proporcionar (*R*)-*N*^{2}-(2-(2,4-dimetoxibencilamino)-4-

fluorofenil)-N^4-(8-fluorocroman-4-il)pirimidin-2,4,5-triamina que se usó directamente.

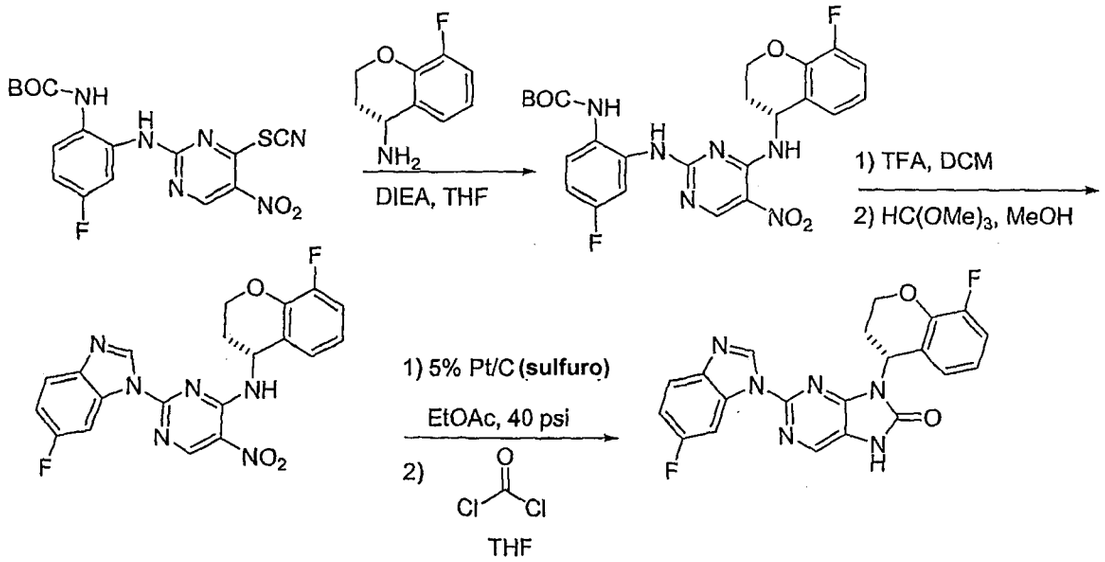
[00293] A una solución agitada del material anterior en THF (5 mL) se agregó CDI (12 mg). Después de 18 horas, se agregaron salmuera y EtOAc, y la mezcla se separó. La capa orgánica se evaporó y se purificó mediante cromatografía en columna (eluida con 4 % MeOH/DCM) para proporcionar el producto del título (14 mg). ^{1}H NMR (300 MHz, $CDCl_3$+5%CD_3OD): δ 7.8 (s, 1H), 7.3 (s, 1H), 7.1 (d, 1H), 6.9 (m, 2H), 6.7-6.2 (m, 6H), 5.7 (dd, 1H), 4.5 (m, 1H), 4.2 (m, 1H), 4.1 (s, 2H), 3.8 (s, 3H), 3.7 (s, 3H), 2.8 (m, 1H), 2.2 (m, 1H).

[00294] 2-(5-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona.

[00295] Una mezcla de (*R*)-2-(2-(2,4-dimetoxibencilamino)-4-fluorofenilamino)-9-(8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona (14 mg) y TFA (1 mL) se agitó durante 60 minutos cuando se agregó trietil silano (0.5 mL). La solución resultante se agitó a temperatura de la sala durante 16 horas, luego los disolventes se redujeron *in vacuo* para proporcionar (*R*)-2-(2-amino-4-fluorofenilamino)-9-(8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona que se utilizó tal como estaba.

[00296] Una cantidad catalítica de *p*-TsOH se agregó a una solución de la amina anterior en ortoformiato de trimetilo (2 mL). La mezcla se agitó a temperatura de la sala durante 15 horas, luego los disolventes se redujeron y el material resultante se repartió en porciones entre DCM y salmuera, y se separó. El producto crudo se purificó mediante cromatografía en columna (eluida con 5 % MeOH/DCM) para proporcionar el compuesto del título (9 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.9 (s, 1H), 8.3 (s, 1H), 7.8 (dd, 1H), 7.4 (d, 1H), 7.1 (m, 2H), 6.8 (m, 2H), 5.9 (dd, 1H), 4.7 (m, 1H), 4.4 (td, 1H), 2.9 (m, 1H), 2.4 (m, 1H).

[00297] Síntesis de 2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona.



[00298] **(R)-*terc*-Butil 4-fluoro-2-(4-(8-fluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino)fenilcarbamato**. *terc*-Butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato (2.0 g) se agregó a una solución de clorhidrato de (*R*)-8-fluorocroman-4-amina (1.1 gram) y *N*,*N*-diisopropiletilamina (2.2 mL) en THF (anhidro, 50 mL). La mezcla se agitó durante 6 horas a temperatura de la sala, luego se repartió en porciones entre agua y EtOAc, y se separó. La capa acuosa se lavó con más EtOAc y los orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron *in vacuo* para proporcionar el producto del título en 94% de rendimiento. MH^+ = 515, 459 (-/Bu).

[00299] **2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-N-((*R*)-8-fluorocroman-4-il)-5-nitropirimidin-4-amina**. Una solución recién preparada de 30% TFA/DCM (100 mL) se agregó a (R)-*terc*-butil 4-fluoro-2-(4-(8-fluorocroman-4-ilamino)-5-nitropirimidin-2-ilamino)fenilcarbamato y la solución se agitó a temperatura de la sala durante 60 minutos. Los disolventes se retiraron *in vacuo* para proporcionar (*R*)-N2-(2-amino-5-

fluorofenil)-N4-(8-fluorocroman-4-il)-5-nitropirimidin-2,4-diamina, que se empleó sin purificación posterior. $MH^+ = 415$.

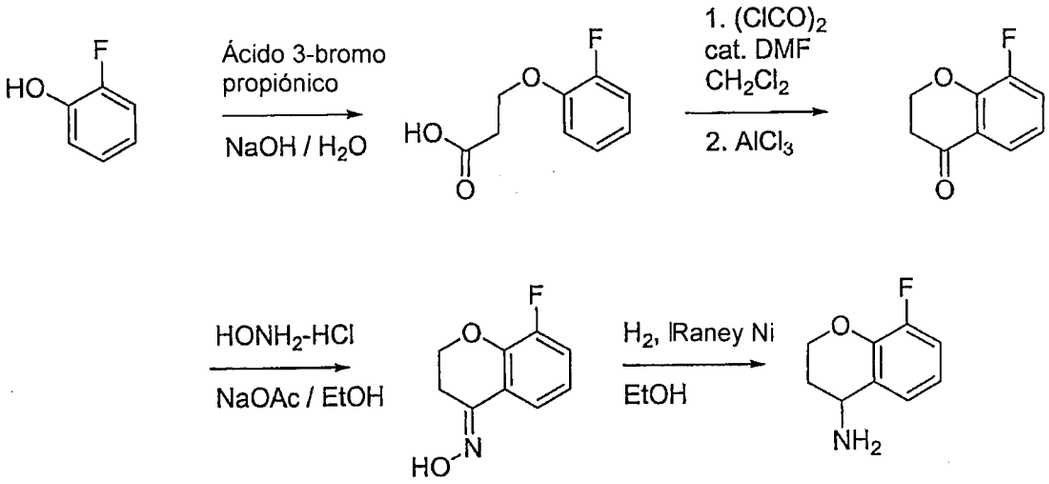
[00300] A la diamina anterior se agregó MeOH (50 mL) y ortoformiato de trimetilo (50 mL). La mezcla se agitó durante 30 minutos a temperatura de la sala, y los disolventes se retiraron *in vacuo* para proporcionar 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-N-((R)-8-fluorocroman-4-il)-5-nitropirimidin-4-amina cruda en 94% de rendimiento (2 pasos). $MH^+ = 425$.

[00301] 2-(6-Fluoro-1*H*-benzo[*d*]imidazol-1-il)-9-((*R*)-8-fluorocroman-4-il)-7*H*-purin-8(9*H*)-ona. A una solución de la 2-(6-fluoro-1*H*-benzo[*d*] imidazol-1-il)-*N*-((*R*)-8-fluorocroman-4-il)-5-nitropirimidin-4-amina en EtOAc (20 mL) se agregó 5 mol% de platino, 5% en polvo de carbón activado, sulfuro, 0.5% S (como sulfuro) (45.6 mg). La mezcla se roció con argón, se transfirió a un aparato de hidrogenación Parr, luego se sometió a una secuencia de purga/llenado con hidrógeno (repetida 5X). La mezcla se hidrogenó durante 18 horas a 40 psi. La filtración a través de una almohadilla de celita y la concentración del filtrado produjeron 2-(6-fluoro-1*H*-benzo[*d*]imidazol-1-il)N^4-((*R*)-8-fluorocroman-4-il)pirimidin-4,5-diamina cruda, que se empleó sin purificación posterior. $MH^+ = 425$.

[00302] A una solución de la diamina anterior en THF (50 mL) se agregó gota a gota 20% de una solución de fosgeno en tolueno a temperatura de la sala. Inmediatamente se formó un precipitado marrón. Se mantuvo la agitación durante 30 minutos más a temperatura de la sala, y los disolventes se retiraron *in vacuo* para proporcionar el compuesto del título. El producto crudo se cristalizó de EtOAc caliente para proporcionar 1.10 g (53%, 2 pasos) del compuesto del título como un sólido blancuzco. El tratamiento con 5 mL de metanol y 5 mL de HCl (concentrado, acuoso) produjo 1.25 g de la sal clorhidrato como un sólido blancuzco. ^{1}H-NMR (300 MHz, CD_3OD) δ 10.0 (s, 1H), 8.4 (s, 1H), 7.9-7.8 (m, 2H), 7.5 (td, 1H), 7.0-6.9

(m, 1H), 6.7-6.6 (m, 2H), 5.9 (dd, 1H), 4.6 (dt, 1H), 4.4 (td, 1H), 2.9-2.8 (m, 1H), 2.4-2.3 (m, 1H); $MH^+ = 421$.

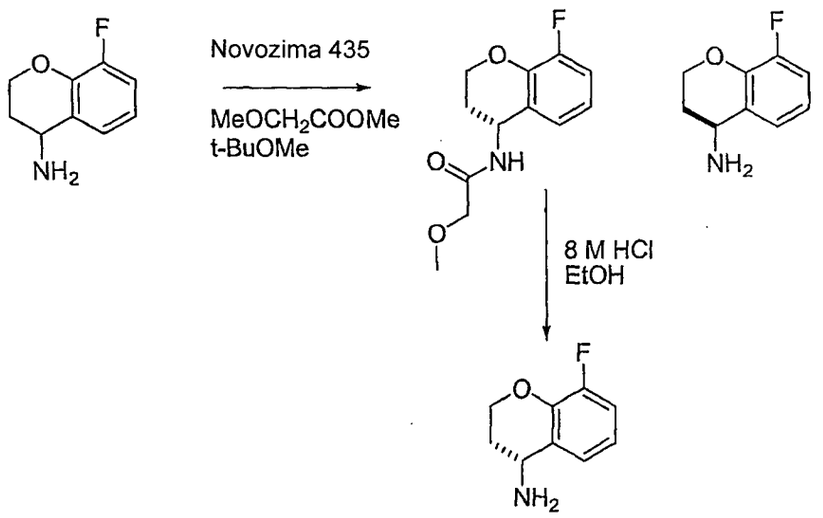
[00303] Ejemplo 29. Síntesis y Resolución de 8-Fluorocroman-4-amina:



[00304] Ácido 3-(2-fluorofenoxi)propanoico. Una mezcla de 2-fluorofenol (15 g), ácido 3-bromopropanoico (20 g) y NaOH (11 g) se hizo refluir en 50mL de agua. La solución se enfrió a temperatura de la sala y se acidificó a pH 2 con 3 M HCl. El precipitado resultante se aisló mediante filtración para proporcionar 9.27 g del compuesto del título como un sólido blanco. El filtrado se extrajo 3 veces con EtOAc para proporcionar 2.5g de compuesto menos puro.

[00305] 8-Fluorocroman-4-ona. Cloruro de oxalilo (8.79 mL) y 1 gota de DMF se agregaron a una solución helada de ácido 3-(2-fluorofenoxi)propanoico (9.27 g) en DCM (50 mL). La solución se agitó a 0 °C durante 2 horas, luego se agregó cloruro de aluminio (7.39g, 55.42mM), y la solución se agitó durante 16 horas a temperatura de la sala. La mezcla se vertió sobre agua helada, y se extrajo tres veces con DCM. Los orgánicos combinados se lavaron con 0.5M NaOH y salmuera, luego se secaron, se evaporaron, y se purificaron por cromatografía en columna (eluyendo con 20% EtOAc/Hex) para producir del compuesto del título (8.20g, 98%).

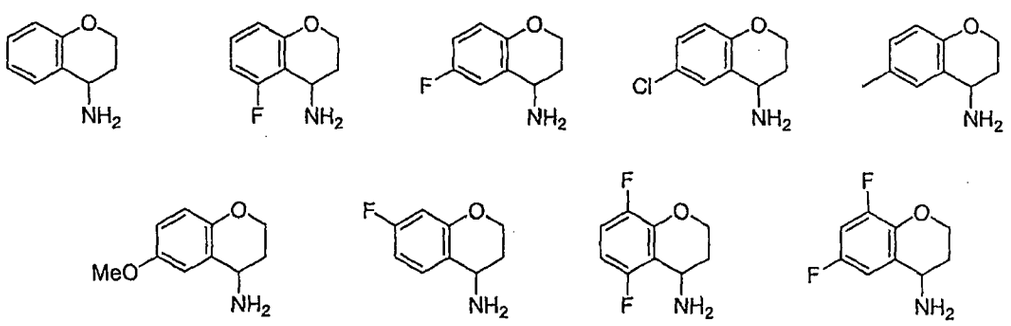
[00306] 8-Fluorocroman-4-amina. Un matraz de fondo redondo se cargó con 8-fluorocroman-4-ona (8.2g), clorhidrato de hidroxilamina (3.78g) y acetato de sodio (4.46g). Se conectó un condensador de reflujo, el matraz se purgó con argón, se agregó EtOH seco (20 mL), y la mezcla se agitó a reflujo durante 18 horas. La solución se enfrió a temperatura de la sala, se diluyó con EtOAc, y se lavó con agua. La fase orgánica se secó, y se evaporó para producir el intermedio 8-fluorocroman-4- ona oxima, la cual se redujo con níquel de Raney en EtOH a 50 PSI para proporcionar la amina del título (4.69g, 57%).



[00307] Resolución de 8-fluorocroman-4-amina. (Procedimiento basado en la Solicitud de los Estados Unidos publicada el 2004/0157739). Una mezcla de 8-fluorocroman-4-amina (3.40 g), metil 2-metoxiacetato (2.44 g) y novozima 435 (Aldrich, 0.68 g) en *terc*-butil metil éter anhidro (75mL) se calentó a reflujo bajo argón durante 2 horas (tiempo en el cual la relación de producto acilado a no acilado fue de 1:1 mediante HPLC). El sólido que se formó luego de enfriar se recogió mediante filtración y se disolvió en EtOAc. La mezcla se filtró para retirar el biocatalizador, y se lavó una vez con 0.5M HCl para retirar cualquier (S)-amina remanente. El disolvente se evaporó, y el producto se recristalizó de *terc*-butil metil éter para proporcionar (R)-N-(8-fluorocroman-4-il)-2-metoxiacetamida (0.78 g). El disolvente de reacción y el agua madre de recristalización se lavó 3 veces con 0.5 M HCl y se concentró para proporcionar más (R)-N-(8-

fluorocroman-4-il)-2-metoxiacetamida (0.83 g). Las capas acuosas ácidas combinadas se basificaron con NaOH y se extrajeron con DCM para proporcionar (*S*)-8- fluorocroman-4-amina (1.6g). Una solución de (*R*)-N-(8-fluorocroman-4-il)-2-metoxiacetamida (0.78g) en 8M HCl en EtOH (50mL) se calentó a reflujo durante 4 horas. Los disolventes se retiraron de la mezcla de reacción enfriada, el sólido resultante se tomó en 50 mL de 0.5M NaOH, se puso en una capa de sal con $NaCl_{(s)}$, y se extrajo 4 veces con DCM para proporcionar (R)-8-fluorocroman-4-amina (0.48 g (87%)). El % ee se verificó mediante HPLC quiral: método Chiralcel OD-H (columna analítica 0.46 x 25 cm, Daicel Chemical Industries): isocrático 5 % (0.05% TFA/EtOH) 95 % (0.05 % TFA/Hex), Rt = 7.2 minutos (*S*)-enantiómero, Rt = 9.2 minutos (*R*)-enantiómero.

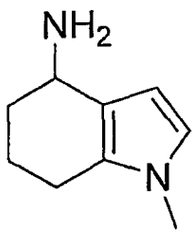
[00308] Ejemplo 30. Croman-4-amina, 5-fluorocroman-4-amina, 6-fluorocroman-4-amina, 6-clorocroman-4-amina, 6-metilcroman-4-amina, 6-metoxicroman-4-amina, 7-fluorocroman-4-amina, 5,8-difluorocroman-4-amina, y 6,8-difluorocroman-4-amina.



[00309] Estas aminas se prepararon mediante procedimientos descritos en Ejemplo 29 para la síntesis de 8-fluorocroman-4-amina. Las correspondientes croman-4-onas se obtuvieron comercialmente como intermedios avanzados para la síntesis de croman-4-amina, 6-fluorocroman-4-amina, 6-clorocroman-4-amina, 6-metilcroman-4-amina, y 6-metoxicroman-4-amina. Para la síntesis de 5-fluorocroman-4-amina, el intermedio 5-fluorocroman-4-ona se obtuvo usando procedimientos de GB 2355264, los cuales proporcionaron también 7-fluorocroman-4-ona. 7-Fluorocroman-4-ona pudo usarse en la síntesis de 7-fluorocliroman-4-

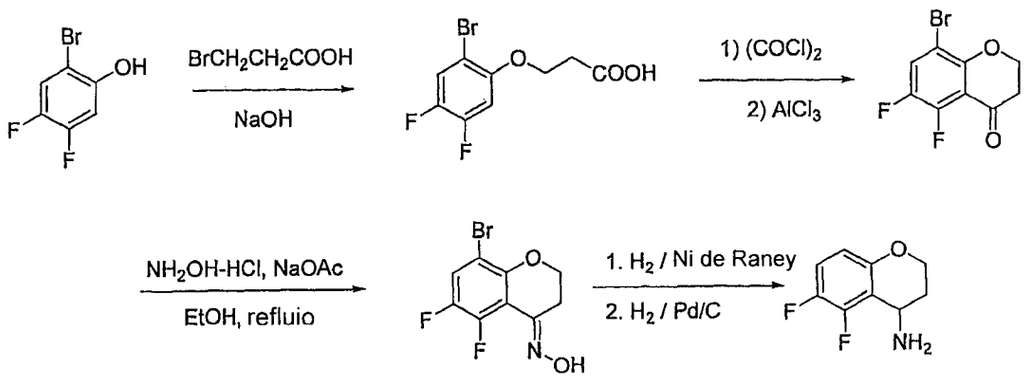
amina. Croman-4-amina, 5-fluorocroman-4-amina, 6-fluorocroman-4-amina, 7-fluorocroman-4-amina, 5,8-difluorocroman-4-amina, y 6,8-difluorocroman-4-amina se resolvieron mediante el procedimiento descrito en Ejemplo 29 para la resolución de 8-fluorocroman-4-amina.

[00310] Ejemplo 31. 1-Metil-4,5,6,7-tetrahidro-1H-indol-4-amina.



[00311] El compuesto del título se obtuvo de 1-metil-6,7-dihidro-1H-indol-4(5H)-ona (Heterociclos (1984), 22, 2313) mediante el procedimiento descrito en Ejemplo 29 que se utilizó para obtener 8-fluorocroman-4-amino de 8-fluorocroman-4-ona.

[00312] Ejemplo 32. Síntesis de 5,6-Difluorocroman-4-amina:



[00313] Ácido 3-(2-bromo-4,5-difluorofenoxi)propanoico. Una solución de 1.68 g de NaOH (42 mmol) en 5 mL de agua se agregó lentamente a la suspensión de 2.29 mL (20 mmol) de 2-bromo-4,5-difluorofenol y 3.07 g (20 mmol) de ácido 3-bromopropiónico. La mezcla se calentó a 100 °C en un baño de aceite durante 5 horas, y luego se dejó enfriar a temperatura de la sala. Se agregó agua para disolver completamente cualquier matrial sólido, y la mezcla de reacción se acidificó con HCl concentrado. El

producto se extrajo en éter (3 veces), y las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se evaporaron para producir 3.7 g (66%) del compuesto del título como un sólido marrón claro. ^1H NMR (300 MHz, $CDCl_3$): δ 7.4 (t, 1H), 6.8 (q, 1H), 4.3 (t, 2H), 2.9 (t, 2H).

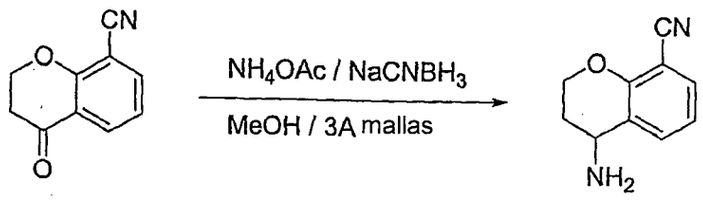
[00314] 8-Bromo-5,6-difluoro-2,3-dihidrocromen-4-ona. Cloruro de oxalilo (1.7 mL, 20 mmol) se agregó a la solución de 2.8 g (10 mmol) de ácido 3-(2-bromo-4,5-difluorofenoxi)-propanoico en 40 mL de DCM anhidro, seguido por una gota de DMF. Luego de 1.5 horas, se conectó un tubo de secamiento, y la solución se enfrió en un baño de agua helada. Se agregó $AlCl_3$ (1.5 g, 11 mmol), y la solución rojo oscuro se dejó alcanzar lentamente la temperatura de la sala, agitando simultáneamente durante 16 horas. La mezcla se vertió en hielo, y la capa orgánica se separó. La capa acuosa se extrajo con DCM dos veces. Las capas orgánicas combinadas se lavaron con 0.5 N NaOH y salmuera, luego se secaron sobre Na_2SO_4 y se concentraron. Cromatografía en columna de este residuo con hexano y EtOAc proporcionó 1.9 g del compuesto del título como un sólido blancuzco (73%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.6 (t, 1H), 4.65 (t, 2H), 2.85 (t, 2H).

[00315] 8-Bromo-5,6-difluoro-2,3-dihidrocromen-4-ona oxime. A una solución de 8-bromo-5,6-difluoro-2,3-dihidrocromen-4-ona (7.2 mmol) en 40 mL de etanol se agregó clorhidrato de hidroxilamina (0.55 g, 7.9 mmol) y acetato de sodio (0.65 g, 7.9 mmol). Esta mezcla se calentó a reflujo durante 20 horas. La mezcla se enfrió, se diluyó con EtOAc, se lavó con agua y salmuera, y luego se secó sobre Na_2SO_4. La concentración del disolvente proporcionó el compuesto del título como un sólido blanco (1.9 g). ^1H NMR (300 MHz, 10% CD_3OD in $CDCl_3$): δ 7.3 (t, 1H), 4.2 (t, 2H), 2.9 (t, 2H).

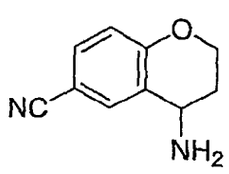
[00316] 5,6-Difluoro-3,4-dihidro-2H-cromen-4-amina. Níquel de Raney (5 mL de suspensión en agua) se agregó a una solución de 8-bromo-5,6-

difluoro-2,3-dihidrocromen-4-ona oxime (1.9 g) en 200 mL MeOH. La mezcla se hidrogenó a 50 psi durante 24 horas para proporcionar 8-bromo-5,6-difluoro-3,4-dihidro-2H-cromen-4-amina. Se agregó Pd/C (0.3 g) a la mezcla, y se reasumió la hidrogenación a 50 psi durante 4 horas. El compuesto del título se obtuvo luego de la filtración y concentración *in vacuo*. ^{1}H NMR (300 MHz, 10% CD_3OD in $CDCl_3$): δ 7.15 (q, 1H), 6.6 (m, 1H), 4.6 (bm, 1H), 4.25 (bm, 2H), 2.2-2.4 (m, 2H).

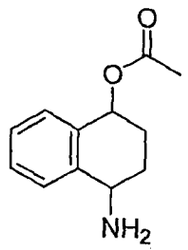
[00317] Ejemplo 33. Síntesis de 4-Amino-3,4-dihidro-2H-cromeno-8-carbonitrilo:



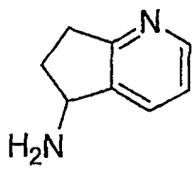
[00318] 4-Amino-3,4-dihidro-2H-cromeno-8-carbonitrilo. Una mezcla de 260 mg de 4-oxo-3,4-dihidro-2H-cromeno-8-carbonitrilo (preparado de 2-hidroxibenzonitrilo mediante el procedimiento descrito en Ejemplo 29), acetato de amonio (1.2 g), y mallas moleculares de 3 A (1.5 g) en 10 mL de metanol se agitó durante 5 días. La mezcla se filtró a través de celita y el filtrado se concentró *in vacuo*. El residuo crudo se trató con 100 mL de 1 M HCl y se extrajo con éter etílico (3 X 100 mL). La capa acuosa se basificó a pH 10 con NaOH saturado y se extrajo con DCM (3 X 100 mL). Las capas DCM combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, y se concentraron *in vacuo* para proporcionar 150 mg del compuesto del título.



[00319] 4-Amino-3,4-dihidro-2H-cromeno-6-carbonitrilo. El compuesto del título se preparó de 6-ciano-4-cromanona (Syntech) mediante el mismo procedimiento que se describió en Ejemplo 33.

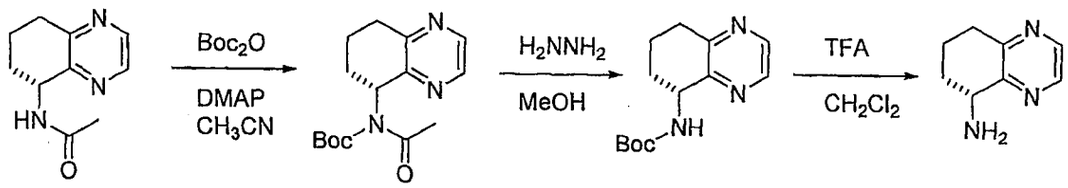


[00320] 4-Amino-1,2,3,4-tetrahidronaftalen-1-il acetato. El compuesto del título se preparó de 4-oxo-1,2,3,4-tetrahidronaftalen-1-il acetato (Tetrahedron: Asymmetry 2001, 12, 2283) mediante el mismo procedimiento que se describió en Ejemplo 33.



[00321] 6,7-Dihidro-5H-ciclopenta[b]piridin-5-amina. El compuesto del título se preparó como se describe en WO 03/045924.

[00322] Ejemplo 34. Síntesis de (R)-5,6,7,8-Tetrahidroquinoxalin-5-amina:



[00323] (R)-*terc*-Butil acetil(5,6,7,8-tetrahidroquinoxalin-5-il) carbamato. Una solución que contenía 483 mg de (R)-N-(5,6,7,8-tetrahidroquinoxalin-5-il)acetamida (J. Org. Chem. (2003), 68, 3546) en acetonitrilo (20 mL) se trató con BoC_2O (3 g) y DMAP (5 mg). La mezcla se calentó a 60 °C durante 1.5 horas y luego se concentró *in vacuo*. Cromatografía en columna (50% EtOAc / hexanos) proporcionó 293 mg del compuesto del título.

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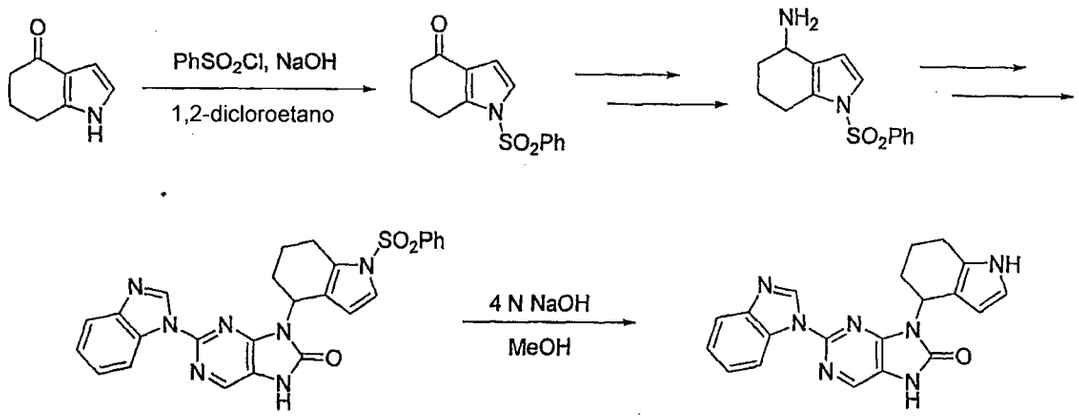
[00324] (R)-*terc*-Butil 5,6,7,8-tetrahidroquinoxalin-5-ilcarbamato. Una solución de (R)-*terc*-butil acetil(5,6,7,8-tetrahidroquinoxalin-5-il) carbamato (293 mg) en metanol (10 mL) se trató con hidrato de hidrazina (0.5 mL) durante 1.5 horas. La mezcla se diluyó con EtOAc y se lavó dos veces con cloruro de sodio acuoso saturado. La capa orgánica se separó, se secó con sulfato de sodio, y se concentró *in vacuo* para proporcionar 238 mg del compuesto del título.

[00325] 2,3-Dihidrobenzofuran-3-amina. A la solución de benzofuran-3(2H)-ona oxime (1.0 g, obtenida de benzofuran-3(2H)-ona disponible en el comercio mediante el procedimiento descrito para la síntesis de 4-fluorobenzofuran-3(2H)-ona oxime de 4-fluorobenzofuran-3(2H)-ona) en 50 mL MeOH, se agregó 10% de paladio sobre carbón activo (0.1 g). La mezcla se vació, luego se llenó con H_2 tres veces. Finalmente el oxime se redujo bajo un balón de H_2 durante 24 horas. La mezcla se filtró a través de una almohadilla de celita, y la torta se lavó con MeOH dos veces. Luego de retirar los disolventes bajo vacío, se obtuvieron 0.99 g de residuo marrón-amarillo como la amina deseada. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 1H), 7.19 (t, 1H), 6.94 (t, 1H), 6.82 (d, 1H), 4.5-4.7 (m, 1H), 4.64 (s, 1H), 4.1-4.2 (m, 1H).

[00326] (R)-5,6,7,8-Tetrahidroquinoxalin-5-amina. Una solución de (R)-*terc*-butil 5,6,7,8-tetrahidroquinoxalin-5-ilcarbamato (238 mg) en 10 ml de 1:1 TFA / DCM se agitó durante 30 minutos. La mezcla se concentró *in vacuo* para proporcionar el compuesto del título como la sal TFA.

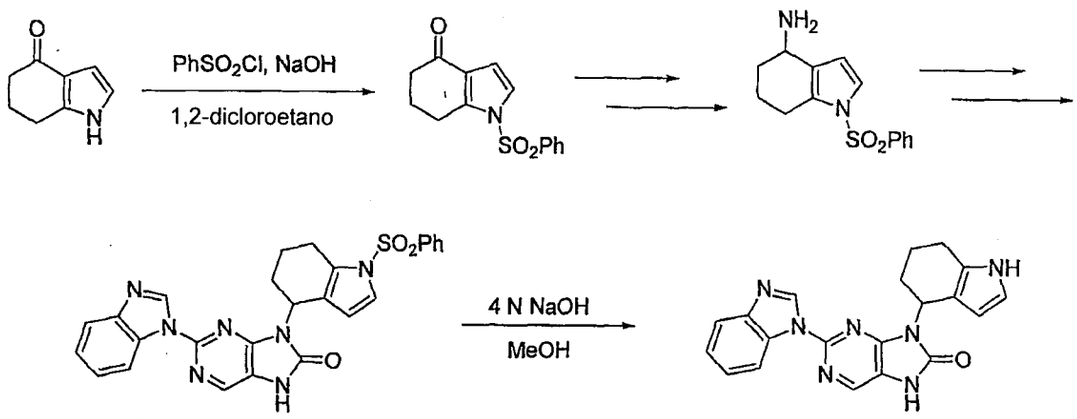
[00327] Ejemplo 35. Síntesis de 2-(1*H*-Benzo[d]imidazol-1-il)-9-(4,5,6,7-tetrahidro-1H-indol-4-il)-7*H*-purin-8(9*H*)-ona:

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[00328] 1-(Fenilsulfonil)-4-oxo-4,5,6,7-tetrahidroindol. A una suspensión de NaOH (4.44 g) en 1,2-dicloroetano (250 mL) se agregó 4-oxo-4,5,6,7-tetrahidroindol (5.0 g). La mezcla se enfrió entonces a 0 °C y se agitó durante 30 minutos, luego de lo cual una solución de cloruro de fenilsulfonilo (5.7 mL) en 1,2-dicloroetano (50 mL) se agregó gota a gota durante un período de 30 minutos. Luego de agitar durante 30 minutos, la mezcla de reacción se dejó alcanzar la temperatura de la sala y se agitó de un día para otro. La reacción se extinguió vertiendo en agua destilada (100 mL). La capa orgánica se separó, y la capa acuosa se extrajo con diclorometano (3 x 50 mL). El extracto orgánico combinado se lavó con agua destilada a neutralidad, se secó sobre $MgSO_4$, y se concentró *in vacuo* para proporcionar 7.0 g del compuesto del título.

[00329] 1-(Fenilsulfonil)-4,5,6,7-tetrahidro-1H-indol-4-amina. El compuesto del título se obtuvo de 1-(fenilsulfonil)-4-oxo-4,5,6,7-tetrahidroindol mediante el procedimiento descrito en Ejemplo 29, que se utilizó para obtener 8-fluorocroman-4-amina de 8-fluorocroman-4-ona.



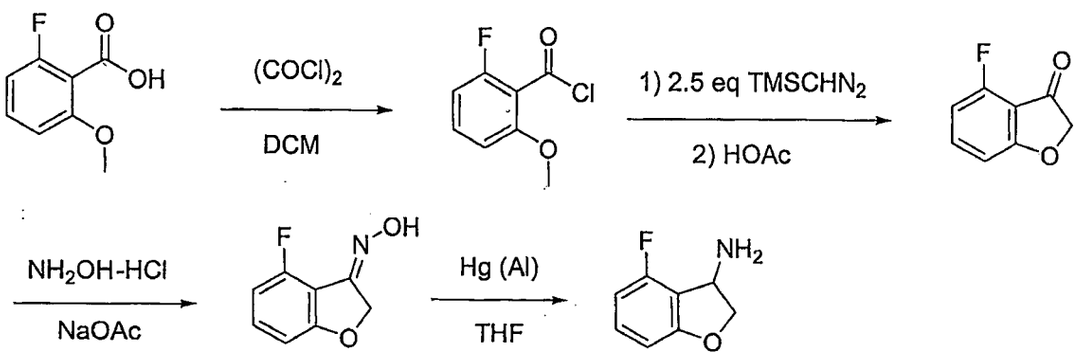
[00328] 1-(Fenilsulfonil)-4-oxo-4,5,6,7-tetrahidroindol. A una suspensión de NaOH (4.44 g) en 1,2-dicloroetano (250 mL) se agregó 4-oxo-4,5,6,7-tetrahidroindol (5.0 g). La mezcla se enfrió entonces a 0 °C y se agitó durante 30 minutos, luego de lo cual una solución de cloruro de fenilsulfonilo (5.7 mL) en 1,2-dicloroetano (50 mL) se agregó gota a gota durante un período de 30 minutos. Luego de agitar durante 30 minutos, la mezcla de reacción se dejó alcanzar la temperatura de la sala y se agitó de un día para otro. La reacción se extinguió vertiendo en agua destilada (100 mL). La capa orgánica se separó, y la capa acuosa se extrajo con diclorometano (3 x 50 mL). El extracto orgánico combinado se lavó con agua destilada a neutralidad, se secó sobre $MgSO_4$, y se concentró *in vacuo* para proporcionar 7.0 g del compuesto del título.

[00329] 1-(Fenilsulfonil)-4,5,6,7-tetrahidro-1H-indol-4-amina. El compuesto del título se obtuvo de 1-(fenilsulfonil)-4-oxo-4,5,6,7-tetrahidroindol mediante el procedimiento descrito en Ejemplo 29, que se utilizó para obtener 8-fluorocroman-4-amina de 8-fluorocroman-4-ona.

[00330] 2-(1*H*-Benzo[d]imidazol-1-il)-9-(1-(fenilsulfonil)-4,5,6,7-tetrahidro-1*H*-indol-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se obtuvo de 1-(fenilsulfonil)-4,5,6,7-tetrahidro-1H-indol-4-amina mediante los procedimientos descritos en Ejemplo 24.

[00331] 2-(1*H*-benzo[*d*]imidazol-1-il)-9-(4,5,6,7-tetrahidro-1*H*-indol-4-il)-7*H*-purin-8(9*H*)-ona. A una solución de 2-(1*H*-benzo[*b*]imidazol-1-il)-9-(1-(fenilsulfonil)-4,5,6,7-tetrahidro-1H-indol-4-il)-7*H*-purin-8(9*H*)-ona (50 mg) en MeOH (1 mL) se agregó 4 N NaOH (1 mL), y la mezcla se hizo refluir de un día para otro y se enfrió. Se retiraron los volátiles bajo presión reducida, y el resultante se neutralizó con 4 N HCl. El precipitado blanco se filtró, se lavó con una pequeña cantidad de agua, y se secó *in vacuo* para proporcionar 36 mg del compuesto del título. ^{1}H NMR (d_6-DMSO) δ 11.6 (s, 1H), 10.7 (s, 1H), 8.86 (s, 1H), 8.27 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.33 (m, 2H), 6.53 (t, J = 2.4 Hz, 1H), 5.64 (t, J = 2.4 Hz, 1H), 5.54 (m, 1H), 2.72 (m, 2H), 2.30 (m, 1H), 2.07 (m, 2H), 1.84 (m, 1H).

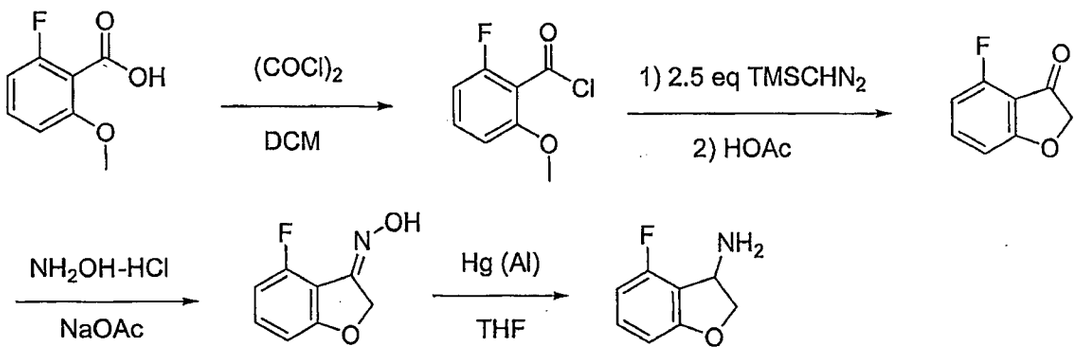
[00332] Ejemplos 36 y 37 (Dihidrobenzofuranos): 2-(1*H*-benzo[d]imidazol-1-il)-9-(2,3-dihidrobenzofuran-3-il)-7*H*-purin-8(9*H*)-ona y 2-(1*H*-benzo[d] imidazol-1-il)-9-(4-fluoro-2,3-dihidrobenzofuran-3-il)-7*H*-purin-8(9*H*)-ona



[00333] Cloruro de 2-fluoro-6-metoxibenzoilo. Cloruro de oxalilo (0.56

[00331] 2-(1*H*-benzo[*d*]imidazol-1-il)-9-(4,5,6,7-tetrahidro-1*H*-indol-4-il)-7*H*-purin-8(9*H*)-ona. A una solución de 2-(1*H*-benzo[*b*]imidazol-1-il)-9-(1-(fenilsulfonil)-4,5,6,7-tetrahidro-1H-indol-4-il)-7*H*-purin-8(9*H*)-ona (50 mg) en MeOH (1 mL) se agregó 4 N NaOH (1 mL), y la mezcla se hizo refluir de un día para otro y se enfrió. Se retiraron los volátiles bajo presión reducida, y el resultante se neutralizó con 4 N HCl. El precipitado blanco se filtró, se lavó con una pequeña cantidad de agua, y se secó *in vacuo* para proporcionar 36 mg del compuesto del título. ^{1}H NMR (d_6-DMSO) δ 11.6 (s, 1H), 10.7 (s, 1H), 8.86 (s, 1H), 8.27 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.33 (m, 2H), 6.53 (t, J = 2.4 Hz, 1H), 5.64 (t, J = 2.4 Hz, 1H), 5.54 (m, 1H), 2.72 (m, 2H), 2.30 (m, 1H), 2.07 (m, 2H), 1.84 (m, 1H).

[00332] Ejemplos 36 y 37 (Dihidrobenzofuranos): 2-(1*H*-benzo[d]imidazol-1-il)-9-(2,3-dihidrobenzofuran-3-il)-7*H*-purin-8(9*H*)-ona y 2-(1*H*-benzo[d] imidazol-1-il)-9-(4-fluoro-2,3-dihidrobenzofuran-3-il)-7*H*-purin-8(9*H*)-ona



[00333] Cloruro de 2-fluoro-6-metoxibenzoilo. Cloruro de oxalilo (0.56 mL, 6.4 mmol) se agregó a la solución de 1.0 g (5.9 mmol) ácido 2-fluoro-6-metoxibenzoico en 5 mL de CH_2Cl_2 anhidro. Luego se agregó una gota de DMF. Pasada una hora, cuando cesó el burbujeo lento, se retiraron los volátiles bajo presión reducida para proporcionar 1.1 g (95%) de cloruro ácido como un líquido amarillo pálido. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (q, 1H), 6.7-6.8 (m, 2H), 3.9 (s, 3H).

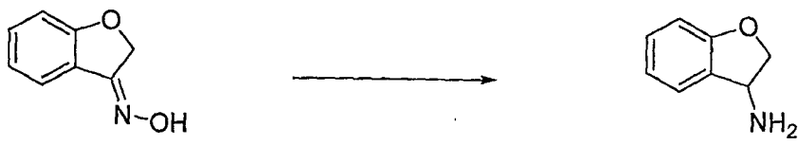
[00334] 4-Fluorobenzofuran-3(2H)-ona. La solución amarilla de (trimetilsilil) diazometano éter (2.0 M, 3.7 mL) se agregó a 0.57 g (3.0 mmol) del cloruro ácido anterior agitando simultáneamente. Luego de 3 horas, se evaporó el disolvente. El residuo amarillo se disolvió en 3 mL de ácido acético (fuerte evolución de gas y calor, se usó un baño de agua para enfriar el matraz durante un minuto), y se agitó durante 15 minutos a temperatura de la sala. Los disolventes se retiraron *in vacuo*, y el residuo rojo se tomó en 2 mL CH_2Cl_2, se lavó con agua dos veces, luego salmuera, y se secó sobre Na_2SO_4. Este producto crudo se purificó mediante cromatografía en columna (eluyendo con 10% EtOAc en hexanos) para producir 0.24 g (53%) 4-fluorobenzofuran-3(2H)-ona como un sólido blanco. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (m, 1H), 6.92 (br d, 1H), 6.71 (t, 1H), 4.65 (s, 2H).

[00335] (Z)-4-Fluorobenzofuran-3(2H)-ona oxima. La cetona anterior (0.70g, 4.6 mmol) se disolvió en 5 ml de alcohol etílico, y luego se agregaron 0.64 g (9.2 mmol) de clorhidrato de hidroxilamina y 0.75 g (9.2 mmol) de acetato de sodio. Esta suspensión se llevó a reflujo durante 1 hora. La mezcla se enfrió a temperatura de la sala, y se agregaron 4 mL de agua para disolver los reactivos en exceso. La filtración por succión y el lavado posterior de la torta sólida con una pequeña cantidad de agua fría proporcionó 0.48 g (63%) del oxime deseado como cristales de agujas blancos. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.38 (q, 1H), 6.6-6.8 (m, 2H), 5.21 (s, 2H).

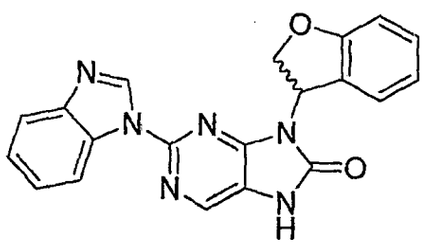
[00336] 4-Fluoro-2,3-dihidrobenzofuran-3-amina. El oxime anterior (0.48 g) se disolvió en 40 mL de THF anhidro bajo argón. Se agregó rápidamente amalgama de aluminio recién preparado (sumergiendo 1 g de hoja de aluminio pulido consecutivamente en solución acuosa al 2% de $HgCl_2$, agua y, finalmente THF), y la mezcla se hizo refluir durante 24 horas bajo argón. Microcápsulas de mercurio brillantes aparecieron en el fondo del matraz. La mezcla se dejó enfriar a temperatura de la sala y se

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filtró a través de una almohadilla de celita. El matraz y la torta sólida se lavaron con THF tres veces, luego con metanol tres veces. El filtrado combinado se evaporó por rotación para producir 0.41g de un sólido amarillo como una mezcla de aproximadamente (determinado por NMR) 20% de la amina deseada con 80% del oxime de partida. Esta mezcla se usó para el siguiente paso sin purificación. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (q, 1H), 6.5-6.7 (m, 2H), 4.8-4.9 (m, 1H), 4.69 (t, 1H), 4.2-4.3 (m, 1H).



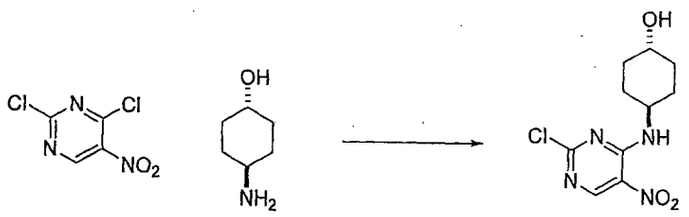
[00337] 2,3-Dihidrobenzofuran-3-amina. A la solución de benzofuran-3(2H)-ona oxime (1.0 g, obtenida de benzofuran-3(2H)-ona disponible en el comercio mediante el procedimiento descrito para la síntesis de 4-fluorobenzofuran-3(2H)-ona oxima de 4-fluorobenzofuran-3(2H)-ona) en 50 mL MeOH se agregó 10% de paladio sobre carbón activo (0.1 g). La mezcla se vació y luego se llenó con H_2 tres veces. Finalmente, el oxime se redujo bajo un balón de H_2 durante 24 horas. La mezcla se filtró a través de una almohadilla de celita, y la torta se lavó con MeOH dos veces. Luego de retirar los disolventes bajo vacío, se obtuvieron 0.99 g de un residuo marrón-amarillo como la amina deseada. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 1H), 7.19 (t, 1H), 6.94 (t, 1H), 6.82 (d, 1H), 4.5-4.7 (m, 1H), 4.64 (s, 1H), 4.1-4.2 (m, 1H).



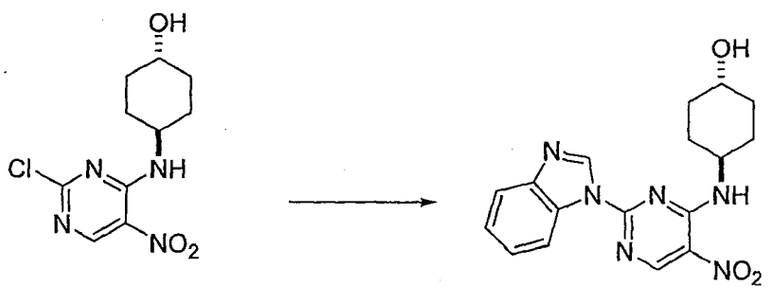
[00338] La anterior 2-(1*H*-benzo[d]imidazol-1-il)-9-(2,3-dihidrobenzofuran-3-il)-7*H*-purin-8(9*H*)-ona racémica puede separarse en una columna quiral CHIRALCEL OD-H (tris(3,5-dimetilfenilcarbamato de celulosa) en un sustrato 5μM de gel de sílice) eluyendo con 85:15

hexanos:etanol (ambos con 0.1% dietilamina). Un enantiómero tiene un tiempo de retención de 25 minutos, el otro 33.5 minutos.

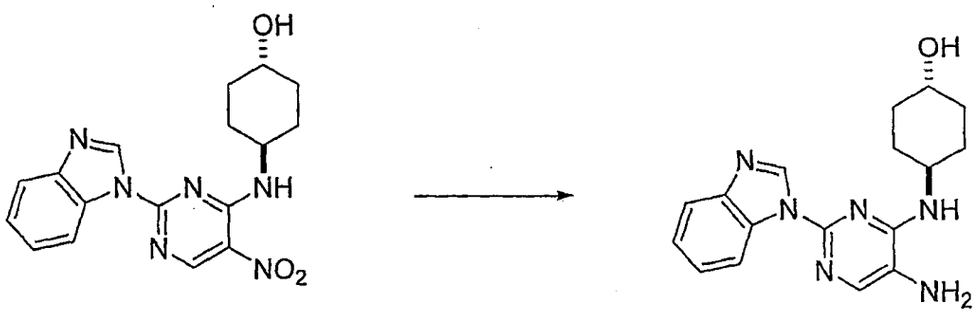
[00339] Síntesis de 2-(1*H*-Benzo[d]imidazol-1-il)-9-(trans-4-hidroxiciclohexil)-7H-purin-8(9*H*)-ona.



[00340] ***trans*-4-(2-Cloro-5nitropirimidin-4-ilamino)ciclohexanol**. Una solución de 2,4-dicloro-5-nitropirimidina (930 mg) en DCM (40 mL) se trató con DIEA (0.9 mL) y *trans*-4-aminociclohexanol (345 mg) a -78 °C durante 6 horas. La mezcla se dejó calentar lentamente a temperatura de la sala y se agitó durante 12 horas más. El disolvente se evaporó y la mezcla cruda se purificó mediante cromatografía en gel de sílice (DCM.EtOAc 70:30) para proporcionar 630 mg del compuesto del título.

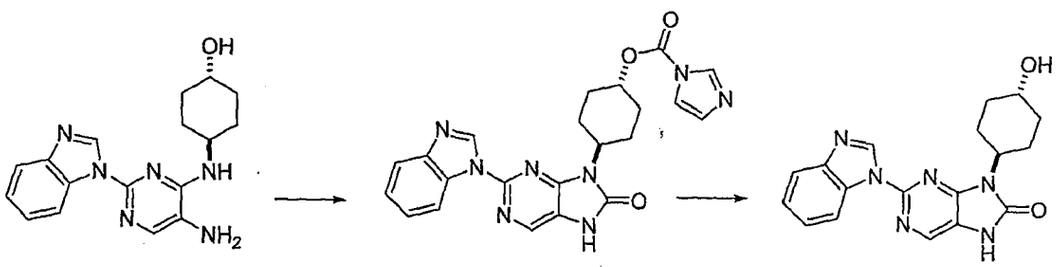


[00341] ***trans*-4-(2-(1*H*-Benzo[d]imidazol-1-il)-5-nitropirimidin-4-ilamino)ciclohexanol**. Una mezcla de *trans*-4-(2-cloro-5nitropirimidin-4-ilamino) ciclohexanol (310 mg), benzimidazol (390 mg), y carbonato de potasio (0.5 g) se calentó en acetonitrilo a 60 °C durante 2 horas. La mezcla se concentró sobre gel de sílice y se purificó mediante cromatografía en columna (DCM:EtO AcMeOH 70:22:8) para producir 350 mg del compuesto del título.



[00342] ***trans*-4-(5-Amino-2-(1*H*-benzo[d]imidazol-1-il)pirimidin-4-ilamino)ciclohexanol**. Una solución de *trans*-4-(2-(1*H*-benzo[d]imidazol-1-il)-5-nitropirimidin-4-ilamino)ciclohexanol (162 mg) en THF (20ml) se trató con una solución de hidrosulfito de sodio (500 mg) y $NaHCO_3$ (500 mg) en 20 mL de agua y se agitó durante 25 minutos. La mezcla se diluyó con 200 mL EtOAc y se lavó dos veces con cloruro de amonio saturado. La fase orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo* para proporcionar 150 mg del compuesto del título.

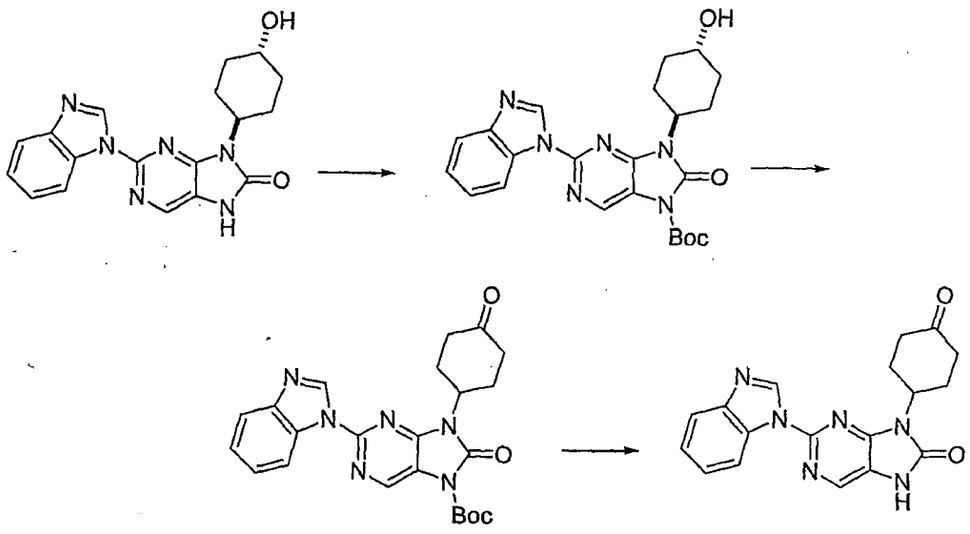
[00343] ***trans*-4-(2-(1*H*-Benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexil 1*H*-imidazol-1-carboxilato**. Una solución de *trans*-4-(5-amino-2-(1*H*-benzo[d]imidazol-1-il)pirimidin-4-ilamino)ciclohexanol (150 mg) en DCM (15mL) se trató con carbonildiimidazol (250 mg) de un día para otro. La mezcla se diluyó con 100 mL de DCM y se lavó con salmuera una vez, luego dos veces con agua. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. La purificación por cromatografía en columna (DCM:EtOAc;MeOH 70:22:8) proporcionó 30 mg del compuesto del título.



[00344] **2-(1*H*-Benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona**. *trans*-4-(2-(1*H*-Benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexil 1H-imidazol-1-carboxilato (30 mg) se disolvió

en DMSO (6 mL) y se trató con 1N HCl (5 ml) a 50 °C durante 3 horas. La mezcla se diluyó con EtOAc y se lavó con salmuera tres veces. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo* para obtener 16 mg del compuesto del título. ^{1}H-NMR (300 MHz, $CDCl_3$) δ10.0 (s, 1H), 8.9 (dd, 1H), 8.2 (s, 1H), 7.9 (dd, 1H), 7.6 (dd, 2H), 4.4 (m, 1H), 4.1 (s, 1H), 2.9 (m, 2H), 2.0 (m, 2H), 1.6 (m, 4H).

[00345] Síntesis de 2-(1*H*-Benzo[d]imidazol-1-il)-9-(4-oxociclohexil)-7*H*-purin-8(9*H*)-ona.

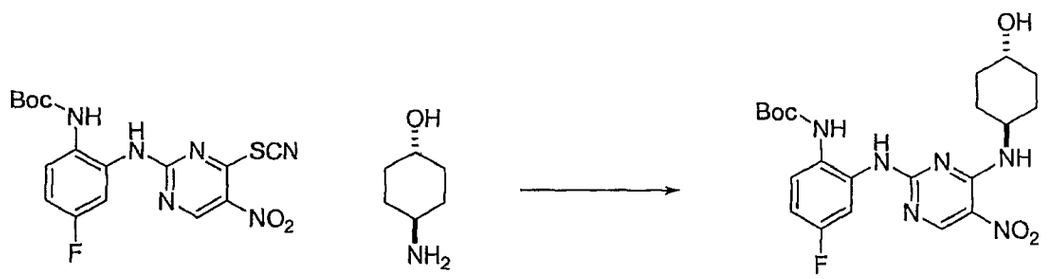


[00346] ***terc*-Butil 2-(1*H*-benzo[d]imidazol-1-il)-9-(trans-4-hidroxiciclohexil)-8-oxo-8,9-dihidropurin-7-carboxilato.** 2-(1*H*-Benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona cruda (16 mg) se disolvió en DCM y se trató con BoC_2O (150 mg) y Et_3N (1 ml). La mezcla se agitó durante 2 horas, luego se diluyó con DCM y se lavó 3 veces con salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. La cromatografía en columna (DCM:EtOAc:MeOH, 70:25:5) proporcionó 17 mg del compuesto del título. Una muestra pura del material de partida, 2-(1*H*-berizo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7H-purin-8(9*H*)-ona, pudo obtenerse mediante desprotección del compuesto del título con 1:1 TFA / DCM durante una hora, y tratando luego el material resultante con 10% HCl metanólico durante 1 hora más, seguida por concentración *in vacuo*.

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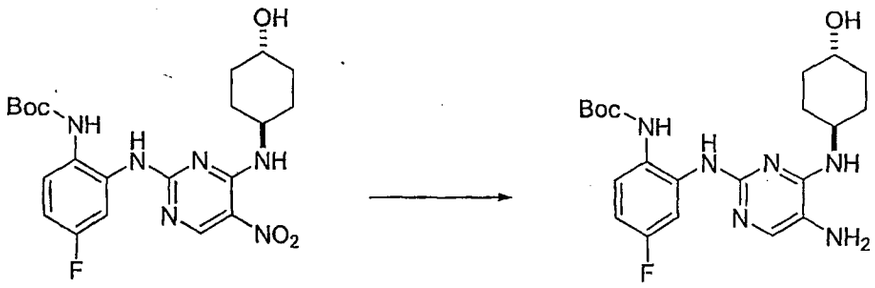
[00347] 2-(1*H*-Benzo[d]imidazol-1-il)-9-(4-oxociclohexil)-7*H*-purin-8(9*H*)-ona. Una solución de cloruro de oxalilo (6.4 mg) en DCM (0.5 ml) se enfrió a - 60 °C y se trató con una solución de DMSO (8 mg) en DCM (0.5 ml). La mezcla de reacción se agitó durante 2 minutos, luego se trató con una solución de *terc*-butil 2-(1*H*-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-8-oxo-8,9-dihidropurin-7-carboxilato (4 mg) en DCM (0.5 ml). Luego de 15 minutos, se agregó trietilamina (0.4 mL) y la mezcla se agitó a temperatura de la sala durante 30 minutos. La mezcla se diluyó con 10 mL DCM y se lavó con 15 mL de agua. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. El residuo se purificó mediante cromatografía en columna para proporcionar 2.3 mg de *terc*-butil 2-(1*H*-benzo[d]imidazol-1-il)-8-oxo-9-(4-oxociclohexil)-8,9-dihidropurin-7-carboxilato, el cual se desprotegió con TFA/DCM (6 ml, 1:1) durante 1 hora. La mezcla se concentró y el residuo se trituró con éter dietílico para proporcionar 1.8 mg del compuesto del título. ^{1}H- NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.5(dd, 1H), 8.4 (s, 1H), 7.9 (dd, 1H), 7.4 (m, 2H), 4.9 (m, 1H), 3.0 (m, 2H), 2.6 (m, 4H), 2.3(m, 2H).

[00348] Síntesis de 2-(6-Fluoro-1*H*-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona.

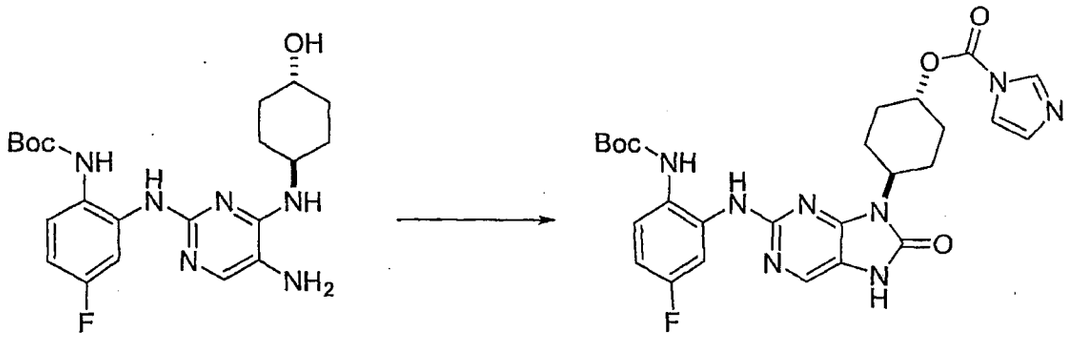


[00349] 4-Fluoro-2-(4-(*trans*-4-hidroxiciclohexilamino)-5-nitropirimidin-2-ilamino)fenilcarbamato. Carbonato de potasio (105 mg) se agregó a una mezcla agitada de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenil-carbamato (101 mg) en acetonitrilo (5 ml), seguido por la adición de *trans*-4-hidroxiciclohexilamina (44 mg). La

mezcla de reacción se agitó durante 16 horas, luego se diluyó con DCM y se lavó con agua y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo* para proporcionar 110 mg del compuesto del título.

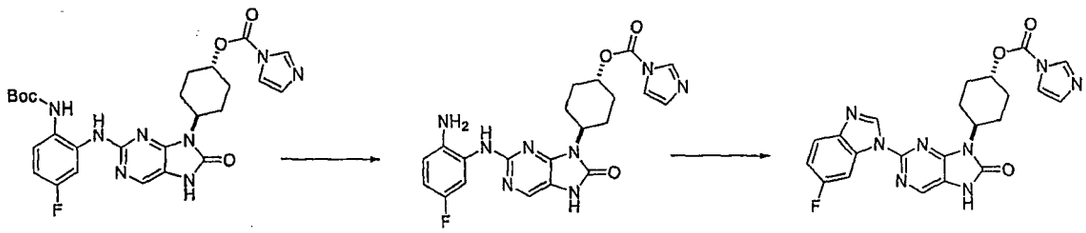


[00350] ***terc*-Butil 2-(5-amino-4-(*trans*-4-hidroxiciclohexilamino) pirimidin-2-ilamino)-4-fluorofenilcarbamato.** Una solución de *terc*-butil 4-fluoro-2-(4-(*trans*-4-hidroxiciclohexilamino)-5-nitropirimidin-2-ilamino) fenilcarbamato (110 mg) en THF (30 mL) se trató con una mezcla que contenía hidrosulfito de sodio (600 mg en 20 ml H2O) y bicarbonato de sodio (10 ml, saturado). La mezcla resultante se agitó por 5 minutos, durante los cuales cambió el color de amarillo a casi incoloro. Se agregó cloruro de sodio saturado, y la mezcla se extrajo con EtOAc dos veces. Las capas orgánicas combinadas se lavaron con cloruro de sodio saturado y se separaron. La fase orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo* para proporcionar 111 mg del compuesto del título.

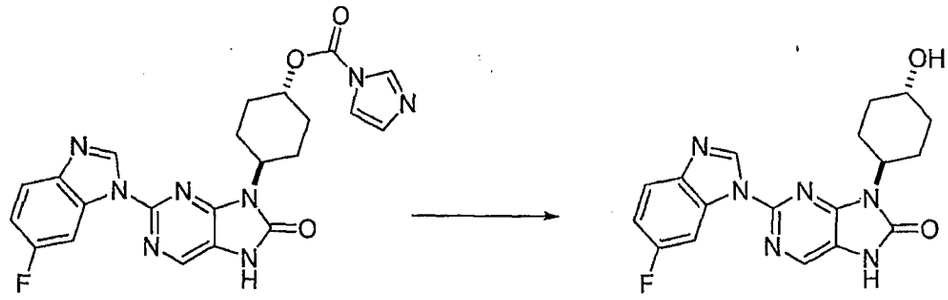


[00351] ***trans*-4-(2-(2-(*terc*-Butoxicarbonil)-5-fluorofenilamino)-8-oxo-7,8-dihidropurin-9-il)ciclohexil 1H-imidazol-1-carboxilato.** Una solución de *terc*-butil 2-(5-amino-4-(*trans*-4-hidroxiciclohexilamino)pirimidin-2-ilamino)-4-fluorofenilcarbamato (111 mg) en DCM (10 mL) se trató con carbonildiimidazol de un día para otro. La mezcla de reacción se diluyó

con DCM (10 ml) y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. La cromatografía en gel de sílice proporcionó 100 mg del compuesto del título.



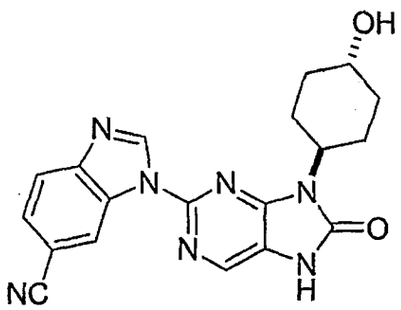
[00352] ***trans*-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexil 1H-imidazol-1-carboxilato**. Una solución de *trans*-4-(2-(2-(*terc*-butoxicarbonil)-5-fluorofenilamino)-8-oxo-7,8-dihidropurin-9-il)ciclohexil 1H-imidazol-1-carboxilato (100 mg) en TFA/DCM (18 ml, 1:1) se agitó durante 1 hora. La mezcla se concentró *in vacuo* para proporcionar 95 mg de material. Este material se disolvió en THF (30 ml) y se trató con $CH(OCH_3)_3$ (1 ml), seguido por ácido p-toluenosulfónico (5 mg). La mezcla se agitó durante 3 horas, se diluyó con EtOAc (100 ml) y se lavó tres veces con salmuera. La capa orgánica se secó sobre Na_2SO_4, y le disolvente se concentró para proporcionar 22 mg del compuesto del título.



[00353] **2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona**. Una solución de *trans*-4-(2-(6-fluoro-1H-berizo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexil 1H-imidazol-1-carboxilato (30 mg) en DMSO (5 ml) se trató con HCl concentrado (1 ml). La mezcla se calentó a 50 °C durante 3 horas. La mezcla se diluyó con EtOAc y se basificó con 3N NaOH (10 ml). La capa orgánica se lavó tres veces con salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró para proporcionar 20 mg del compuesto del título. ^{1}H-NMR

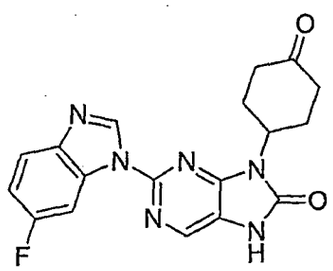
(300 MHz, CD_3OD) δ 10.5 (s, 1H), 8.8 (dd, 1H), 8.6 (s, 1H), 8.1 (dd, 1H), 7.7 (td, 1H), 4.6 (m, 1H), 4.7 (m, 1H), 4.0 (m, 1H), 2.7 (m, 2H), 2.3 (m, 2H), 2.1 (m, 2H), 1.7 (m, 2H).

[00354] Síntesis de 3-(9-(*trans*-4-Hidroxiciclohexil)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo.



El compuesto del título pudo obtenerse de 4-(2,4-dimetoxibencilamino)-3-(4,5-diaminopirimidin-2-ilamino)benzonitrilo utilizando los mismos procedimientos descritos para los síntesis de 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7H-purin-8(9*H*)-ona de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino) fenilcarbamato. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.8 (s, 1H), 9.1(s, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 7.8 (d, 1H), 4.4 (m, 1H), 3.8 (m, 1H), 2.5 (q, 2H), 2.2 (d, 2H), 1.9 (d, 2H), 1.5 (q, 2H).

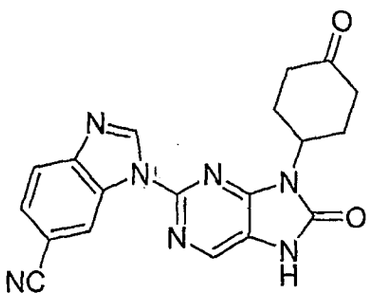
[00355] Síntesis de 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(4-oxociclohexil)-7H-purin-8(9*H*)-ona.



[00356] El compuesto del título pudo obtenerse de 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona utilizando el mismo procedimiento descrito para la síntesis de 2-(1*H*-

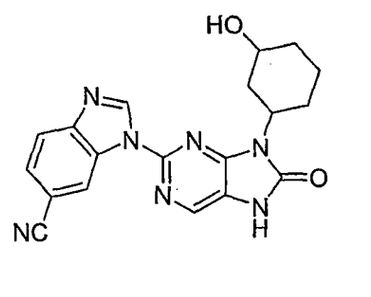
benzo[d]imidazol-1-il)-9-(4-oxociclohexil)-7*H*-purin-8(9*H*)-ona de 2-(1*H*-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.8 (s, 1H), 9.2(s, 1H), 9.1 (s, 1H), 7.6 (dd, 1H), 7.8 (dd, 1H), 4.8 (m, 1H), 2.8 (m, 2H), 2.5 (m, 4H), 2.1 (m, 2H).

[00357] Síntesis de 3-(8-Oxo-9-(4-oxociclohexil)-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo.



[00358] El compuesto del título pudo obtenerse de 3-(9-(*trans*-4-hidroxiciclohexil)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d] imidazol-5-carbonitrilo utilizando los mismos procedimientos descritos para los síntesis de 2-(1*H*-benzo[d]imidazol-1-il)-9-(4-oxociclohexil)-7*H*-purin-8(9*H*)-ona de 2-(1*H*-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.3 (s, 1H), 9.2(s, 1H), 8.5 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 4.6 (m, 1H), 2.9 (m, 2H), 2.6 (m, 4H), 2.2 (m, 2H).

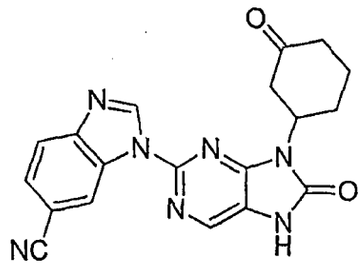
[00359] Síntesis de 3-(9-(3-Hidroxiciclohexil)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo.



El compuesto del título pudo obtenerse de 4-(2,4-dimetoxibencilamino)-3-(4,5-diaminopirimidin-2-ilamino)benzonitrilo y 3-hidroxiciclohexilamina utilizando los mismos procedimientos descritos para los síntesis de 2-(6-

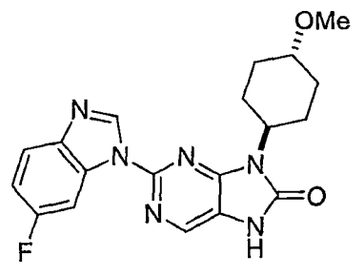
fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.4 (S, 1H), 9.2 (s, 1H), 8.4 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 4.6 (m, 1H), 3.9 (m, 1H), 2.5 (m, 2H), 2.2 (m, 2H), 2.1 (m, 2H), 1.6 (m, 2H).

[00360] Síntesis de 3-(8-Oxo-9-(3-oxociclohexil)-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo.



El compuesto del título pudo obtenerse de 3-(9-(3-hidroxiciclohexil)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo utilizando los mismos procedimientos descritos para los síntesis de 2-(1*H*-benzo[d]imidazol-1-il)-9-(4-oxociclohexil)-7*H*-purin-8(9*H*)-ona de 2-(1*H*-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7*H*-purin-8(9*H*)-ona. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.2 (s, 1H), 8.6(s, 1H), 8.5 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 5.0 (m, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 2.9 (m, 2H), 2.6 (m, 2H), 2.3 (m, 2H).

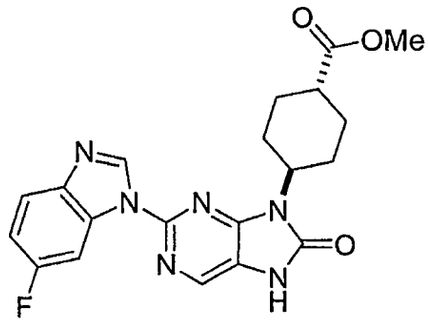
[00361] Síntesis de 2-(6-Fluoro-1H-berizo[d]imidazol-1-il)-9-(*trans*-4-metoxiciclohexil)-7*H*-purin-8(9*H*)-ona.



Una solución de 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-7H-purin-8(9*H*)-ona (112 mg) en DCM se trató con

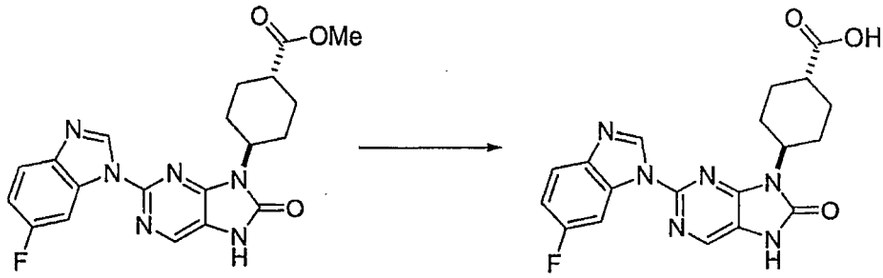
exceso de BoC_2O y trietilamina hasta que el análisis TLC indicó que el material de partida se había consumido (4 horas). La mezcla se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró. El residuo resultante se disolvió en THF, se trató con exceso de yodometano, y luego NaH (10 equivalentes). La mezcla se agitó durante 6 horas y se extinguió mediante la adición de cloruro de amonio saturado. El intermedio se extrajo con EtOAc, se secó, y se concentró. Cromatografía en gel de sílice (70:25:5 DCM:EtOAc:MeOH) proporcionó *terc*-butil 2-(6-fluoro-1H-benzo[d] imidazol-1-il)-9-(*trans*-4-metoxiciclohexil)-8-oxo-8,9-dihidropurin-7-carboxilato puro, el cual se desprotegió en 1:1 TFA / DCM durante 16 horas y se concentró *in vacuo* para obtener el compuesto del título. Se obtuvo la sal HCl tratando una solución metanólica (10 mL) con 0.5 mL de HCl concentrado, seguido por evaporación del disolvente. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.3 (dd, 1H), 8.1 (s, 1H), 7.6 (dd, 1H), 7.1 (td, 1H), 4.4 (m, 1H), 3.8 (m, 1H), 2.5 (m, 2H), 2.1 (m, 2H), 1.9 (m, 2H), 1.5 (m, 2H).

[00362] Síntesis de *trans*-Metil 4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexanocarboxilato.



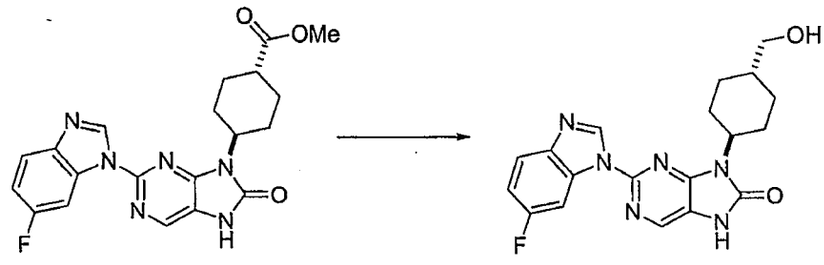
El compuesto del título se obtuvo de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato y metil *trans*-4-aminociclohexanocarboxilato usando procedimientos descritos en Ejemplo 27. H-NMR (300 MHz, $CDCl_3$) δ9.0 (s, 1H), 8.4(s, 1H), 8.3 (dd, 1H), 7.8 (dd, 1H), 7.2 (td, 1H), 4.5 (m, 1H), 2.6 (m, 3H), 2.3 (m, 2H), 2.0 (m, 2H), 1.7 (m, 2H).

[00363] Síntesis de ácido *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8- dihidropurin-9-il)ciclohexanocarboxílico.



Una solución de *trans*-metil 4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexanocarboxilato (5 mg) en THF se trató con una solución acuosa de KOH (35 mg) en 2 mL de agua. La mezcla se calentó a 50 °C durante 12 horas. La mezcla se acidificó con TFA y se concentró. Cromatografía en gel de sílice (60:30:10 DCM:EtOAc:MeOH) proporcionó 4.3 mg del compuesto del título. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.3(dd, 1H), 8.1 (s, 1H), 7.7 (dd, 1H), 7.1 (td, 1H), 4.3 (m, 1H), 2.4 (m, 3H), 2.2 (m, 2H), 1.9 (m, 2H), 1.6 (m, 2H).

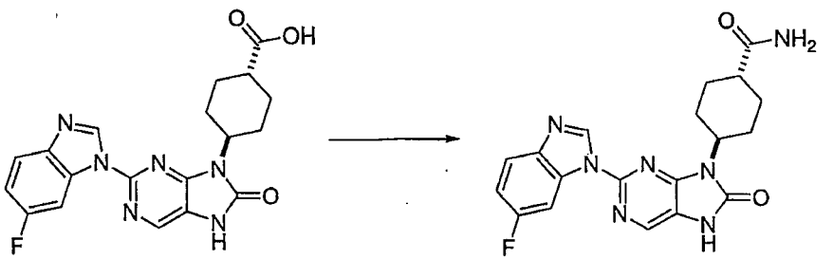
[00364] Síntesis de 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-4-(hidroximetil)ciclohexil)-7*H*-purin-8(9*H*)-ona.



Una solución de *trans*-metil 4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexanocarboxilato (6 mg) en DCM se trató con 10 equivalentes de una solución 1 M THF de $LiAlH_4$ a -10 °C. La mezcla se agitó a -10 °C durante 12 horas y 0 °C durante 2 horas más. La mezcla se extinguió con bicarbonato de sodio acuoso y se extrajo con EtOAc. Cromatografía en gel de sílice proporcionó 3.0 mg del compuesto del título. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.3 (dd, 1H), 8.1 (s,

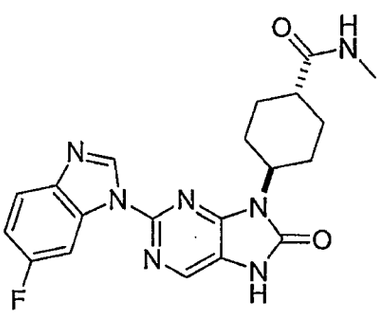
1H), 7.7 (dd, 1H), 7.1 (td, 1H), 4.3 (m, 1H), 3.3 (d, 2H), 2.4 (m, 2H), 1.9 (m, 4H), 1.6 (m, 2H).

[00365] Síntesis de *trans*-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexanocarboxamida.



Una suspensión de ácido *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8- dihidropurin-9-il)ciclohexanocarboxílico (10 mg) en DCM se trató con 6 gotas de DMF, seguido por 3 equivalentes de cloruro de oxalilo. La mezcla se agitó durante 45 minutos, luego se roció con un balón de amoníaco durante 10 minutos. La mezcla se concentró y se purificó mediante HPLC para proporcionar 1.7 mg del compuesto del título. ^{1}H-NMR (300 MHz, CD_3OD) δ 9.1 (s, 1H), 8.3 (dd, 1H), 8.2 (s, 1H) 7.7 (dd, 1H), 7.1 (td, 1H), 4.4 (m, 1H), 2.5 (m, 2H), 2.4 (m, 1H), 2.1 (m, 2H), 1.9 (m, 2H), 1.7 (m, 2H).

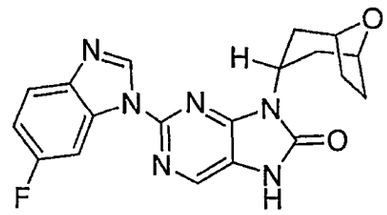
[00366] Síntesis de *trans*-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)-N-metilciclohexanocarboxamida.



El compuesto del título pudo obtenerse de ácido *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)ciclohexano-carboxílico y 2 M metilamina en THF utilizando el mismo procedimiento descrito para la síntesis de *trans*-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-

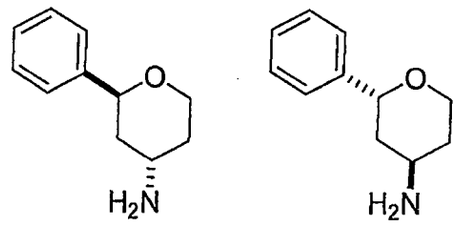
dihidropurin-9-il)ciclohexanocarboxamida. ^{1}H-NMR (300 MHz, $CDCl_3$ with 5 % CD_3OD) δ 9.0 (s, 1H), 8.3 (dd, 1H), 8.2 (s, 1H), 7.7 (dd, 1H), 7.1 (td, 1H), 4.4 (m, 1H), 2.8 (s, 3H) 2.5 (m, 2H), 2.3 (m, 1H), 2.1 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H).

[00367] Síntesis de 9-(8-oxa-biciclo[3.2.1]octan-3-il)-2-(6-fluoro-1H-benzo[d]imidazol-1-il)-7*H*-purin-8(9*H*)-ona.



El compuesto del título se obtuvo de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato y 8-oxa-biciclo[3.2.1]octan-3-amina (WO 2004/041161) utilizando procedimientos descritos en Ejemplo 27. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.4 (bs, 1H), 9.0 (s, 1H), 8.4 (dd, 1H), 8.3 (s, 1H), 7.8 (dd, 1H), 7.1 (td, 1H), 4.9 (m, 1H), 4.6 (m, 2H), 2.9 (m, 2H), 2.2 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H).

[00368] Síntesis de (+/-)-2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-2-fenil-tetrahidro-2H-piran-4-il)-7*H*-purin-8(9*H*)-ona.

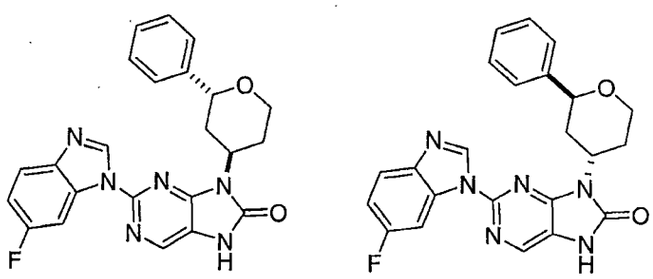


[00369] ***trans*-2-Fenil-tetrahidro-2H-piran-4-amina**. Ácido sulfúrico (80%, 16.5 g) se agregó gota a gota a 0 °C a una mezcla de but-3-en-1-ol (13.6 g) y benzaldehído (10 g). Luego de la adición, la mezcla se agitó a temperatura de la sala durante 16 horas. La mezcla se vertió en agua helada, se basificó (pH 8-10) con 1 N NaOH, se extrajo con EtOAc, se secó, y se concentró. Cromatografía en gel de sílice proporcionó 9 g de *cis*-2-fenil-tetrahidro-2H-piran-4-ol.

[00370] Una solución de *cis*-2-feniltetrahidro-2H-piran-4-ol (1 g) en DCM (20 mL) se enfrió en un baño helado de agua salada y se trató con DIEA (2.2 g) y cloruro de metanosulfonilo (0.7 g) durante 2 horas. La mezcla se diluyó con DCM (50 mL) y se lavó con agua y salmuera. La capa orgánica se secó y se concentró. TLC preparativa proporcionó 0.9 g de *cis*-2-fenil-tetrahidro-2H-piran-4-il metanosulfonato.

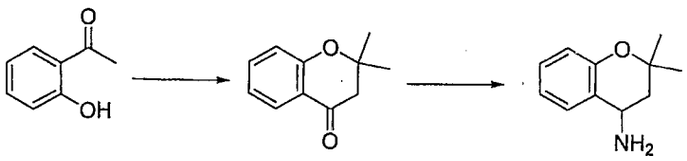
[00371] Una solución de *cis*-2-fenil-tetrahidro-2H-piran-4-il metanosulfonato (0.8 g) en DMF (10 mL) se trató con azida de sodio (0.8 g) y se calentó a 100 °C durante 4 horas. La mezcla se diluyó con DCM (50 mL) y se lavó con agua y salmuera. La capa orgánica se secó y se concentró. TLC preparativa proporcionó 0.5 g de *trans*-4-azido-2-fenil-tetrahidro-2H-pirano.

[00372] El compuesto del título se obtuvo mediante hidrogenación catalítica (Pd-C, H_2) de *trans*-4-azido-2-fenil-tetrahidro-2H-pirano.

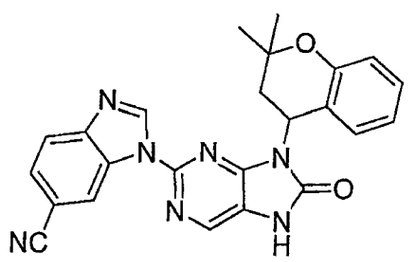


(+/-)-2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(*trans*-2-fenil-tetrahidro-2H-piran-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se obtuvo de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino) fenilcarbamato y *trans*-2-fenil-tetrahidro-2H-piran-4-amina utilizando procedimientos descritos en Ejemplo 27. ^{1}H-NMR (300 MHz, $CDCl_3$ con 5 % CD_3OD) δ 9.0 (s, 1H), 8.2 (dd, 1H), 8.1 (s, 1H), 7.6 (dd, 1H), 7.4 (d, 2H), 7.3 (t, 2H), 7.2 (t, 1H), 7.0 (td, 1H), 5.2 (br s, 1H), 4.7 (m, 1H), 3.9-3.8 (m, 1H), 3.7 (td, 1H), 3.1-2.8 (m, 2H), 2.4 (br d, 1H), 1.7 (br d, 1H).

[00373] Síntesis de 3-(9-(2,2-Dimetilcroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo.

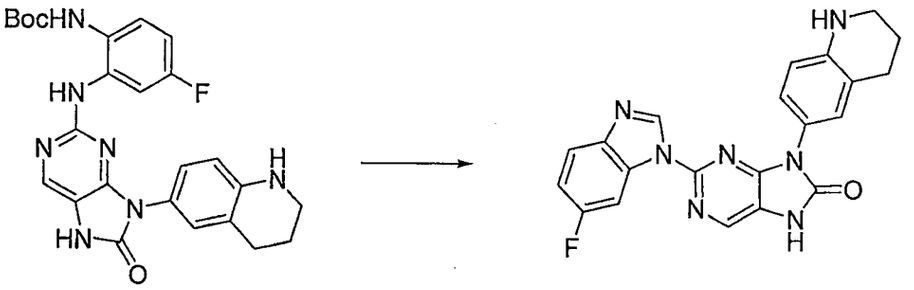


[00374] **2,2-Dimetilcroman-4-amina**. Una solución de 2'-hidroxiacetofenona (5.0 mL), acetona (4.7 mL), y pirrolidina (5.4 mL) en 150 mL de metanol se agitó durante 66 horas. La mezcla se concentró y se trató con HCl acuoso (pH < 1). La capa ácida se extrajo dos veces con éter etílico, la cual se secó y se concentró para proporcionar 2,2-dimetilcroman-4-ona. La 2,2-dimetilcroman-4-ona se disolvió en 300 mL de metanol y se trató con acetato de amonio (65 g) y cianoborohidruro de sodio (2.5 g) durante 24 horas. La mezcla resultante se concentró a 100 mL y se diluyó con 300 mL agua. Se agregó cuidadosamente HCl concentrado hasta que el pH fue inferior a 1, y la mezcla ácida se extrajo con éter dietílico. La fase ácida se basificó con KOH y luego se extrajo dos veces con éter dietílico. Los extractos básicos se secaron y se concentraron para proporcionar el compuesto del título.



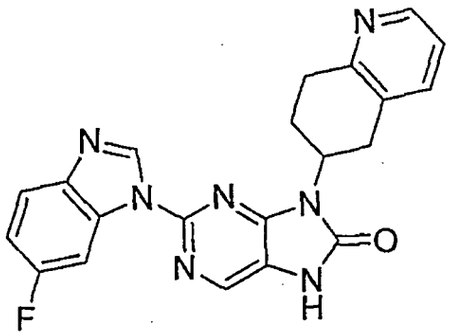
[00375] **3-(9-(2,2-Dimetilcroman-4-il)-8-oxo-8,9-dihidro-7*H*-purin-2-il)-3H-benzo[d]imidazol-5-carbonitrilo**. El compuesto del título se obtuvo de 4-(2,4-dimetoxibencilamino)-3-(4,5-diaminopirimidin-2-ilamino) benzonitrilo y 2,2-dimetilcroman-4-amina utilizando procedimientos descritos en Ejemplo 26. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.6 (s, 1H), 9.0 (s, 1H), 8.5 (bs, 1H), 8.3 (s, 1H), 7.8 (d, 1H), 7.6 (dd, 1H), 7.2 (m, 2H), 6.8 (d, 1H), 6.7 (td, 1H), 5.9 (dd, 1H), 2.9 (t, 1H), 2.2 (dd, 1H), 1.6 (s, 3H), 1.5 (s, 3H).

[00376] Síntesis de 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(1,2,3,4-tetrahidroquinolin-6-il)-7*H*-purin-8(9*H*)-ona.



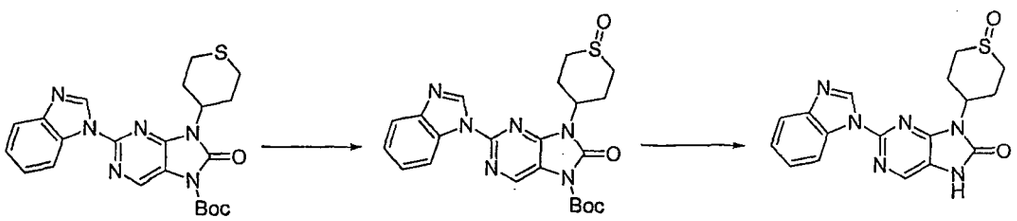
Una solución de *terc*-butil 4-fluoro-2-(8-oxo-9-(1,2,3,4-tetrahidroquinolin-6-il)-8,9-dihidro-7*H*-purin-2-ilamino)fenilcarbamato (obtenido de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato y 1,2,3,4-tetrahidroquinolin-6-amina (*J. Org. Chem.* (2002), 67, 7890) utilizando procedimientos descritos en Ejemplo 27) se agitó durante 45 minutos en 1:1 TFA / DCM y se concentró para proporcionar 2-(2-amino-5-fluorofenilamino)-9-(1,2,3,4-tetrahidroquinolin-6-il)-7*H*-purin-8(9*H*)-ona. La 2-(2-amino-5-fluorofenilamino)-9-(1,2,3,4-tetrahidroquinolin-6-il)-7*H*-purin-8(9*H*)-ona se agitó durante 15 minutos en ortoformiato de trimetilo y se concentró para proporcionar 6-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-8-oxo-7,8-dihidropurin-9-il)-3,4-dihidroquinolin-1 (2H)-carbaldehído, el cual se purificó mediante cromatografía en gel de sílice (2 → 5% MeOH en DCM). Este material se deformiló refluyendo durante 1 hora en 11:2 1 M HCl:MeOH para proporcionar el compuesto del título como la sal HCl. ^{1}H-NMR (300 MHz, CD_3OD) δ 10.0 (s, 1H), 8.4 (s, 1H), 8.4 (dd, 1H), 7.8 (dd, 1H), 7.8 (s, 1H), 7.8 (d, 1H), 7.5 (d, 1H), 7.4 (td, 1H), 3.6 (dd, 2H), 3.1 (t, 2H), 2.2 (m, 2H).

[00377] Síntesis de 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-(5,6,7,8-tetrahidroquinolin-6-il)-7*H*-purin-8(9*H*)-ona.



El compuesto del título se obtuvo de *terc*-butil 4-fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato y 5,6,7,8-tetrahidroquinolin-6-amina (*J. Org. Chem.* (2002), *67*, 7890) utilizando procedimientos descritos en Ejemplo 27. ^{1}H- NMR (300 MHz, CD_3OD) δ 9.3 (s, 1H), 8.6 (d, 1H), 8.5 (dd, 1H), 8.1 (dd, 1H), 7.9 (dd, 1H), 7.4 (td, 1H), 5.2 (m, 1H), 4.2 (dd, 1H), 3.6 (m, 3H), 3.2 (m, 1H), 2.6 (m, 1H).

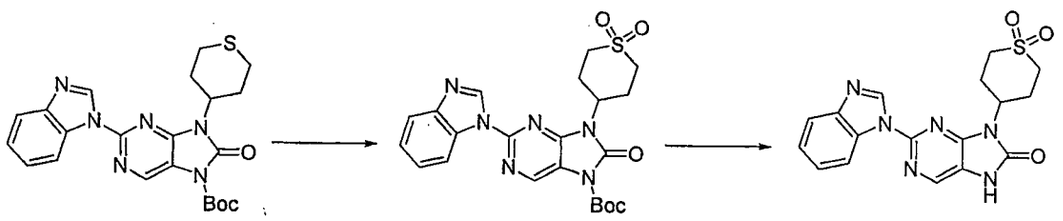
[00378] Síntesis de 2-(1*H*-Benzo[d]imidazol-1-il)-9-(tetrahidro-1-oxido-2H-tiopiran-4-il)-7*H*-purin-8(9*H*)-ona.



[00379] Una solución de *terc*-butil 2-(1*H*-benzo[d]imidazol-1-il)-8-oxo-9-(tetrahidro-2*H*-tiopiran-4-il)-8,9-dihidropurin-7-carboxilato (8 mg, obtenido de tetrahidro-tiopiran-4-ilamina utilizando procedimientos descritos en Ejemplo 16, seguida por protección usando el procedimiento descrito para la síntesis de *terc*-butil 2-(1*H*-benzo[d]imidazol-1-il)-9-(*trans*-4-hidroxiciclohexil)-8-oxo-8,9-dihidropurin-7-carboxilato) en MeOH/H_2O (10ml, 1:1) se trató con KIO_4 (50 mg) y se agitó durante 3 horas. La mezcla de reacción se diluyó con 10 ml de $NaHCO_3$ saturado y se extrajo 3 veces con DCM. Las capas orgánicas se secaron sobre Na_2SO_4, se filtraron, y se concentraron *in vacuo*. La purificación por cromatografía de columna (DCM:EtOAc;MeOH 75:25:5) proporcionó 5.6 mg de *terc*-butil 2-(1*H*-benzo[d]imidazol-1-il)-8-oxo-9-(tetrahidro-1-oxido-2H-tiopiran-4-il)-8,9-

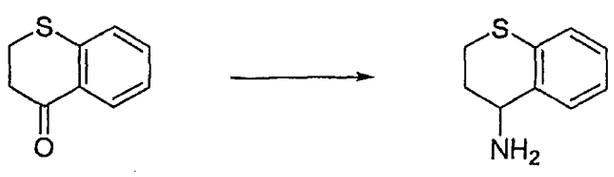
dihidropurin-7-carboxilato. Este material se trató con TFA/DCM (6 ml, 1:1) durante 1 hora y se concentró. La trituración con Et_2O proporcionó 3.3 mg del compuesto del título. ^1H NMR (300 MHz $CDCl_3$) δ 9.1 (br, 1H), 8.5(m, 1H), 8.2 (s, 1H), 7.8 (m, 1H), 7.4 (m, 2H), 4.6 (m, 1H), 3.6 (m, 2H), 2.9 (m, 4H), 2.2 (m, 2H).

[00380] Síntesis de 2-(1*H*-Benzo[d]imidazol-1-il)-9-(tetrahidro-1,1-dioxido-2H-tiopiran-4-il)-7*H*-purin-8(9*H*)-ona.



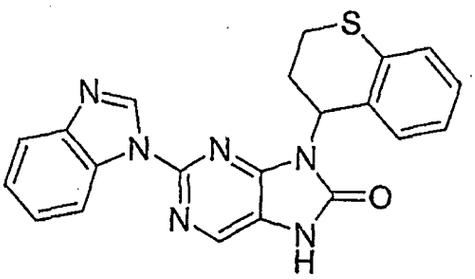
Una solución de *terc*-butil 2-(1*H*-benzo[d]imidazol-1-il)-8-oxo-9-(tetrahidro-2H-tiopiran-4-il)-8,9-dihidropurin-7-carboxilato (8 mg) en DCM (10ml) se trató con MCPBA (13 mg) y se agitó durante 16 horas. La mezcla se lavó 3 veces con salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró *in vacuo*. La purificación por cromatografía en columna (DCM:EtOAc:MeOH 75:25:5) proporcionó 2.2 mg de *terc*-butil 2-(1*H*-benzo[d]imidazol-1-il)-8-oxo-9-(tetrahidro-1,1-dioxido-2H-tiopiran-4-il)-8,9-dihidropurin-7-carboxilato. Este material se trató con TFA/DCM (6 ml, 1:1) durante 1 hora y se concentró. La trituración con Et_2O proporcionó 1.3 mg del compuesto del título. ^1H NMR (300 MHz, $CDCl_3$) δ 9.2 (br, 1H), 8.7 (d, 1H), 7.8 (d, 1H), 7.5 (t, 1H), 7.4 (t, 1H), 4.6 (m, 1H), 3.0-3.5 (m, 6H), 2.2 (m, 2H).

[00381] Síntesis de 2-(1*H*-Benzo[d]imidazol-1-il)-9-(tiocroman-4-il)-7*H*-purin- 8(9*H*)-ona.



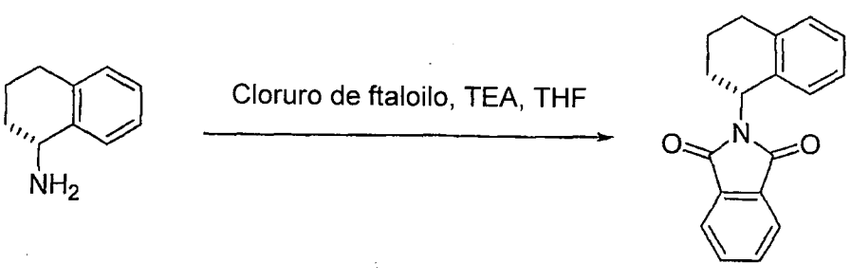
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[00382] Tiocroman-4-amina. A una solución de tiocroman-4-ona (1.6 g) en EtOH (100 ml) se agregó NH_4OAc (8.2 g), la mezcla se calentó a 50 °C durante 35 minutos, luego se enfrió a temperatura de la sala y se trató con $Na(CN)BH_4$ (0.96 g). La mezcla se agitó a temperatura de la sala durante 64 horas, y el disolvente de reacción se retiró *in vacuo*. El residuo se disolvió en EtOAc y se lavó 4 veces con 4N HCl. Los lavados acuosos combinados se basificaron con 3N NaOH, luego se extrayeron 5 veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron para proporcionar 1.4 g del compuesto del título.

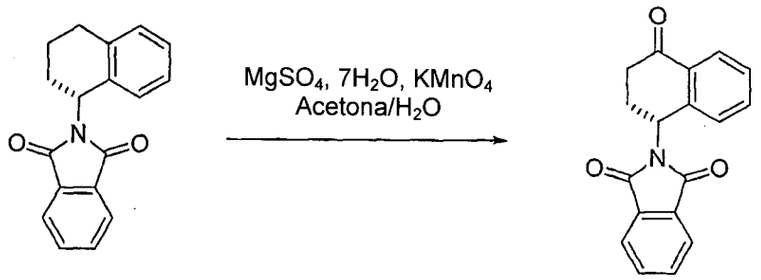


[00383] 2-(1*H*-Benzo[d]imidazol-1-il)-9-(tiocroman-4-il)-7*H*-purin-8(9*H*)-ona. El compuesto del título se sintetizó de tiocroman-4-amina utilizando los procedimientos descritos en Ejemplo 16. ^1H NMR (300 MHz, CD_3OD) δ 9.1 (s, 1H), 8.5 (s, 1H), 8.3 (m, 1H), 7.8 (m, 1H), 7.4 (m, 3H), 7.3 (m, 1H), 7.0-7.2 (m, 2H), 6.0 (m, 1H), 3.4 (m, 2H), 3.1 (m, 1H), 2.6 (m, 1H).

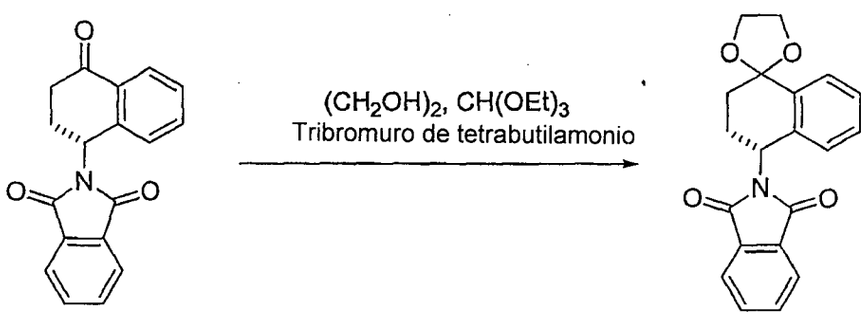
[00384] Síntesis de 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-((*R*)-4-oxo-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona, 2-(6-Fluoro-1*H*-benzo [d]imidazol-1-il)-9-((1*R*,4*R*)-4-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona, y 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-9-((1*R*,4*S*)-4-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona.



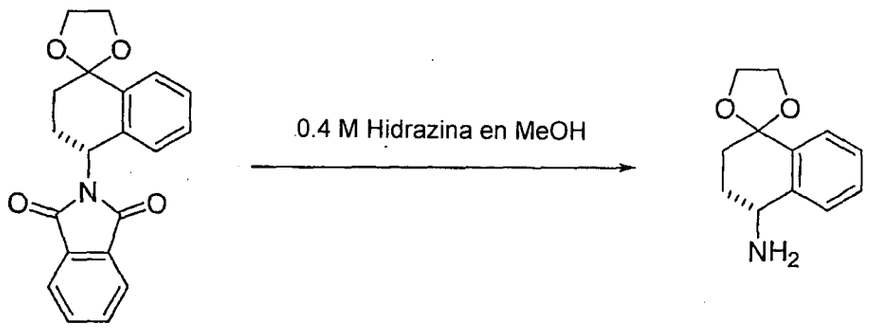
[00385] **(*R*)-2-(1,2,3,4-Tetrahidronaftalen-1-il)isoindolin-1,3-diona.** A una solución de (*R*)-1,2,3,4-tetrahidro-1-naftilamina (6.0 g) en THF (150 mL) a 0 °C se agregó TEA (18.5 mL) y cloruro de ftaloilo (8.2 g), y la mezcla resultante se agitó a temperatura de la sala de un día para otro y 70 °C durante 3 horas. La mezcla se diluyó con CH_2Cl_2, se lavó con $NaHCO_3$ saturado, se secó sobre $MgSO_4$, y se concentró *in vacuo*. El crudo resultante se cromatografió en gel de sílice (EtOAc/hexano, 5/95 a 30/70) para proporcionar 8.2 g del compuesto del título.



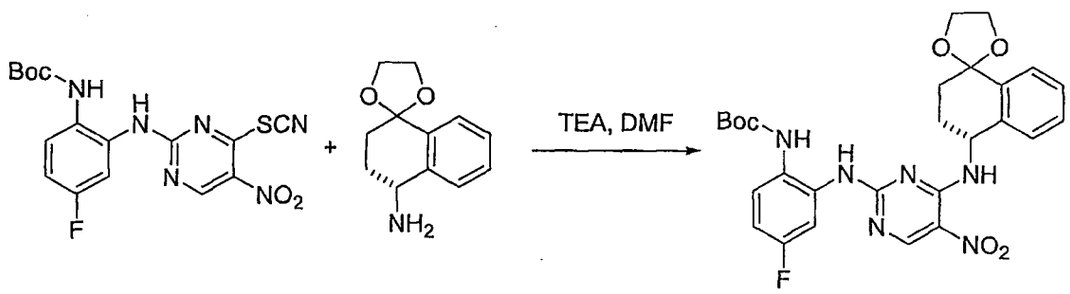
[00386] **(*R*)-2-(4-Oxo-1,2,3,4-tetrahidronaftalen-1-il)isoindolin-1,3-diona.** A una solución de (*R*)-2-(1,2,3,4-tetrahidronaftalen-1-il)isoindolin-1,3-diona (3.9 g) en acetona (60 mL) a 0 °C se agregó $MgSO_4$-$7H_2O$ (11.5 g) y agua (20 mL). Luego se agregó $KMnO_4$ (11.5 g) en porciones durante un período de 2 horas, y se continuó la agitación a temperatura de la sala de un día para otro. El sólido marrón se filtró completamente y el filtrado se trató con metabisulfito de sodio saturado, se filtró, y se extrajo con CH_2Cl_2. La capa orgánica combinada se lavó con agua destilada y salmuera saturada, se secó sobre $MgSO_4$, y se concentró *in vacuo*. El resultante se cromatografió en gel de sílice (EtOAc/hexano, 25/75) para proporcionar 0.14 g del compuesto del título.



[00387] 1,3-Dioxolano de (*R*)-2-(4-oxo-1,2,3, 4-Tetrahidronaftalen-1-il)isoindolin-1,3-diona. A la mezcla de (*R*)-2-(4-oxo-1,2,3,4-tetrahidronaftalen-1-il)isoindolin-1,3-diona (138 mg), ortoformiato de trietilo (0.3 mL), y 1,2-etanodiol (1.5 mL) se agregó tribromuro de tetrabutilamonio (12 mg). La mezcla de reacción se agitó a temperatura de la sala de un día para otro y se calentó a 90 °C durante 3 horas. Luego de enfriar, la mezcla se diluyó con CH_2Cl_2, se lavó con $NaHCO_3$ saturado, agua, y salmuera, se secó sobre $MgSO_4$, y se concentró *in vacuo*. El residuo se purificó mediante PTLC (EtOAc/hexano, 1/2) para proporcionar 150 mg del compuesto del título.

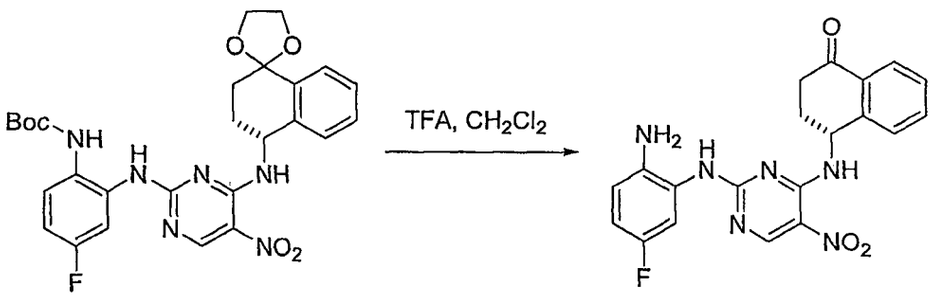


[00388] 1,3-Dioxolano de (*R*)-4-amino-3,4-dihidronaftalen-1(2H)-ona. Una solución de 1,3-dioxolano de (*R*)-2-(4-oxo-1,2,3,4-tetrahidronaftalen-1-il)isoindolin-1,3-diona (145 mg) en 0.4 M de hidrazina metanólica (40 mL) se agitó a temperatura de la sala de un día para otro. El disolvente y el exceso de hidrazina se evaporaron, y se agregó una pequeña cantidad de CH_2Cl_2 al residuo. El sólido blanco se filtró completamente y el filtrado se concentró *in vacuo* para proporcionar 85 mg del compuesto del título.

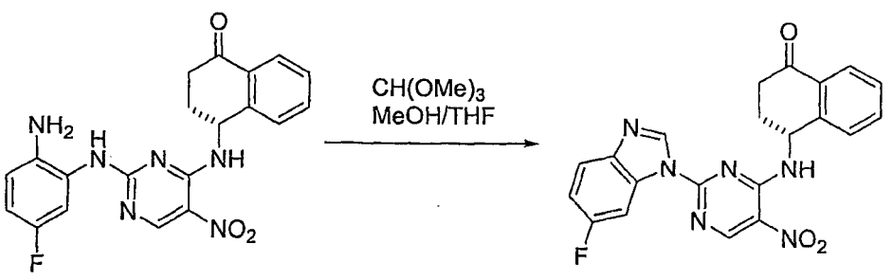


[00389] 1,3-Dioxolano de (*R*)-*terc*-butil 4-fluoro-2-(5-nitro-4-(4-oxo-1,2,3,4-tetrahidronaftalen-1-ilamino)pirimidin-2-

ilamino)fenilcarbamato. Una solución de *terc*-butil 4 fluoro-2-(5-nitro-4-tiocianatopirimidin-2-ilamino)fenilcarbamato (170 mg), 1,3-dioxolano de (*R*)-4-amino-3,4-dihidronaftalen-1(2H)-ona (85 mg), y TEA (0.2 mL) en DMF (5 mL) se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se diluyó con EtOAc, se lavó con salmuera saturada, se secó sobre $MgSO_4$, y se concentró *in vacuo*. El residuo se purificó mediante PTLC (EtOAc/hexano, 50/50) para proporcionar 150 mg del compuesto del título.

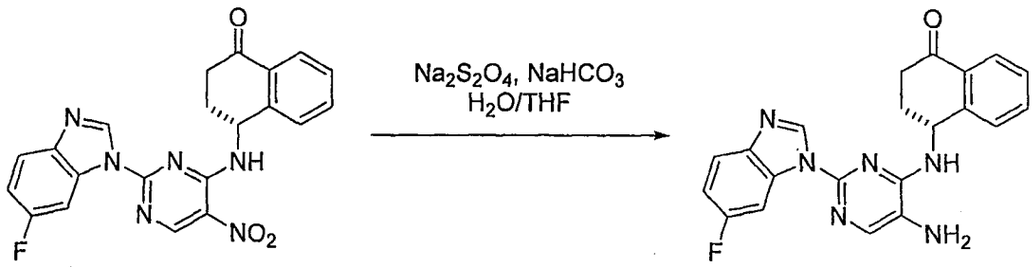


[00390] **(*R*)-4-(2-(2-Amino-5-fluorofenilamino)-5-nitropirimidin-4-ilamino)-3,4-dihidronaftalen-1(2H)-ona**. Una solución de 1,3-dioxolano de (R)-*terc*-butil 4-fluoro-2-(5-nitro-4-(4-oxo-1,2,3,4-tetrahidronaftalen-1-ilamino)pirimidin-2-ilamino)fenilcarbamato (145 mg) y TFA (2.5 mL) en CH_2Cl_2 (5 mL) se agitó a temperatura de la sala durante 1 hora. Se retiraron los volátiles *in vacuo* y el crudo (120 mg) se sometió al siguiente paso sin purificación posterior.

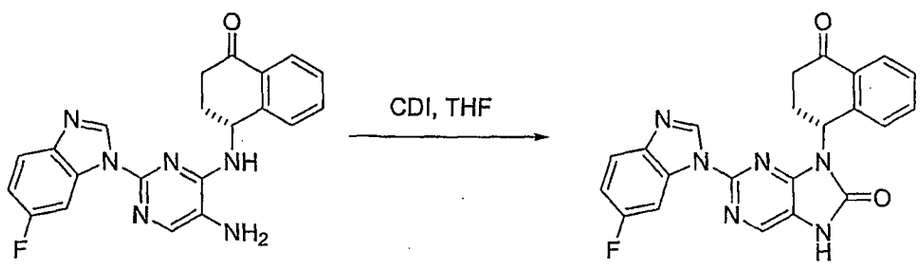


[00391] **(4*R*)-4-(2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-5-nitropirimidin-4-ilamino)-3,4-dihidronaftalen-1(2H)-ona**. Una solución de (*R*)-4-(2-(2-amino-5-fluorofenilamino)-5-nitropirimidin-4-ilamino)-3,4-dihidronaftalen-1(2H)-ona (120 mg) y $CH(OMe)_3$ (2.5 mL) en MeOH/THF (2.5 mL/10 mL) se agitó a temperatura de la sala de un día para otro. Se

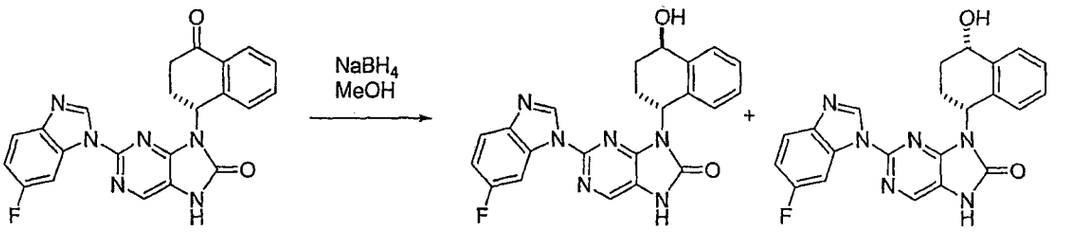
retiraron los volátiles *in vacuo* y el residuo se purificó mediante PTLC (EtOAc) para proporcionar 80 mg del compuesto del título.



[00392] **(4*R*)-4-(5-Amino-2-(6-fluoro-1H-benzo[d]imidazol-1-il) pirimidin-4-ilamino)-3,4-dihidronaftalen-1(2H)-ona**. A la solución de (4*R*)-4-(2-(6-fluoro-1H-benzo[d]imidazol-1-il)-5-nitropirimidin-4-ilamino)-3,4-dihidronaftalen-1(2H)-ona (80 mg) en THF (10 mL) se agregó $Na_2S_2O_4$ (480 mg) y $NaHCO_3$ (240 mg) en H_2O (10 mL), y se continuó la agitación a temperatura de la sala durante 1.5 horas. La mezcla de reacción se diluyó con CH_2Cl_2, se lavó con salmuera saturada, se secó sobre $MgSO_4$, y se concentró *in vacuo*. El crudo (32 mg) se sometió al siguiente paso sin purificación posterior.



[00393] **2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-((*R*)-4-oxo-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona**. Una solución de (4*R*)-4-(5-amino-2-(6-fluoro-1H-benzo[d]imidazol-1-il)pirimidin-4-ilamino)-3,4-dihidronaftalen-1(2H)-ona (32 mg) y CDI (100 mg) en THF (6 mL) se agitó a temperatura de la sala de un día para otro y se hizo refluir durante 2.5 horas. Se retiraron los volátiles *in vacuo* y el residuo se purificó mediante HPLC preparativa para proporcionar 9 mg del compuesto del título como la sal TFA. ^{1}H NMR (CD_3OD) δ 9.20 (s, 1H), 8.36 (s, 1H), 8.20 (m, 1H), 7.68 (m, 1H), 7.58-7.47 (m, 3H), 7.20-7.14 (m, 2H), 6.10 (m, 1H), 3.09-2.93 (m, 3H), 2.49 (m, 1H); MS (MH^+) 415.1.



[00394] 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-((1*R*,4*R*)-4-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona y 2-(6-Fluoro-1H-benzo[d]imidazol-1-il)-9-((1*R*,4*S*)-4-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona. A una solución de 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-9-((R)-4-oxo-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona (6 mg) en MeOH (2.5 mL) a 0 °C se agregó $NaBH_4$ (4.5 mg), y se continuó la agitación a 0 °C durante 3 horas. La reacción se extinguió mediante la adición de NH_4Cl saturado y se extrajo con CH_2Cl_2. Los extractos orgánicos combinados se secaron sobre $MgSO_4$ y se concentraron *in vacuo*. El residuo se purificó mediante HPLC preparativa para proporcionar los compuestos del título como las sales TFA. 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-9-((1*R*,4*R*)-4-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona. 3 mg, R_f= 0.28 (MeOH/DCM, 5/95); ^{1}H NMR (CD_3OD) δ 8.97 (s, 1H), 8.30 (s, 1H), 7.80 (d, 1H), 7.66 (dd, 1H), 7.56 (dd, 1H), 7.30 (t, 1H), 7.13 (m, 2H), 6.95 (d, 1H), 5.85 (dd, 1H), 5.11 (dd, 1H), 2.63 (m, 1H), 2.43 (m, 1H), 2.32 (m, 1H), 1.94 (m, 1H); MS (MH^+) 417.0. 2-(6-fluoro-1H-benzo[d]imidazol-1-il)-9-((1*R*,4*S*)-4-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)-7*H*-purin-8(9*H*)-ona. 2 mg, R_f= 0.33 (MeOH/DCM, 5/95); ^{1}H NMR (CD_3OD) δ 9.01 (s, 1H), 8.33 (s, 1H), 8.00 (m, 1H), 7.67-6.94 (m, 6H), 5.72 (m, 1H), 4.91 (m, 1H), 2.99 (m, 1H), 2.42-2.05 (m, 3H); MS (MH^+) 417.0.

Análisis de cinasa Jak3

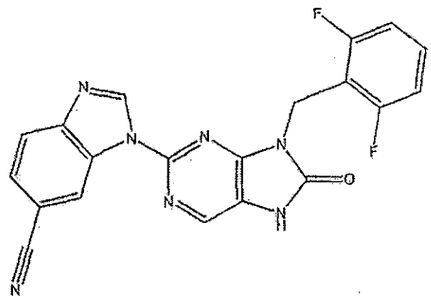
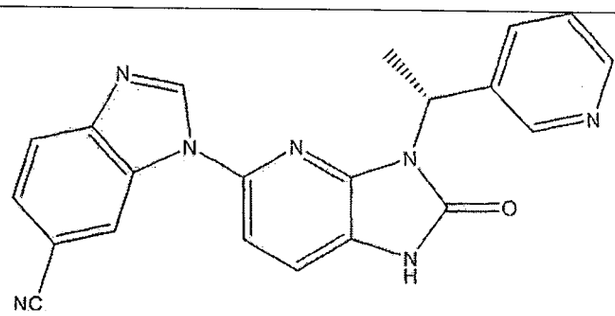
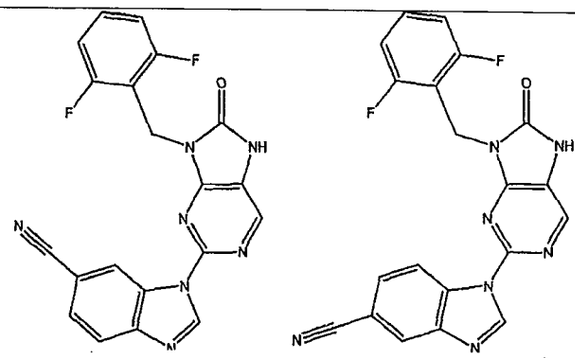
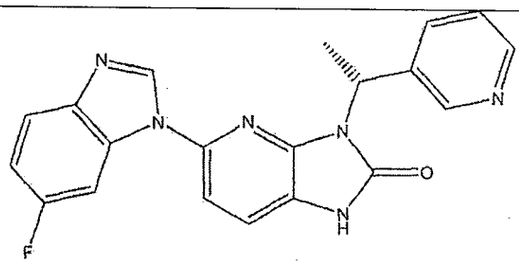
[00395] ADnc de Jak3 humana se amplificó mediante PCR. Un fragmento que codificaba el dominio catalítico de Jak3 (508aa a 1124aa) se ligó con

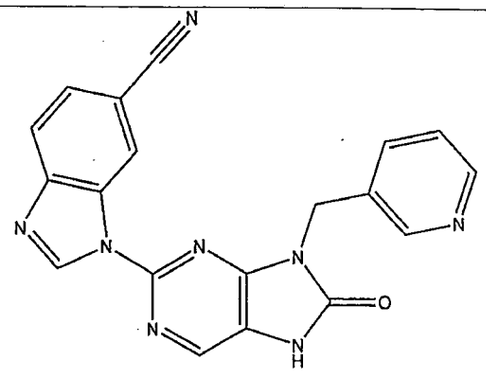
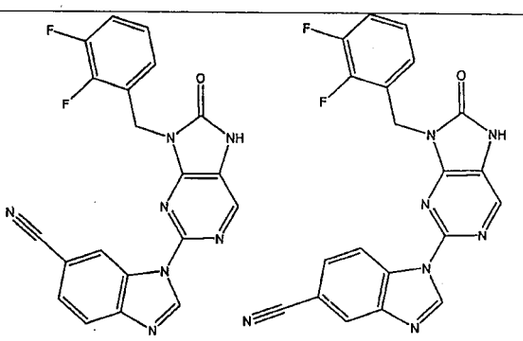
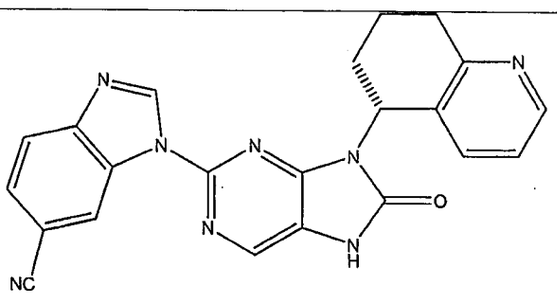
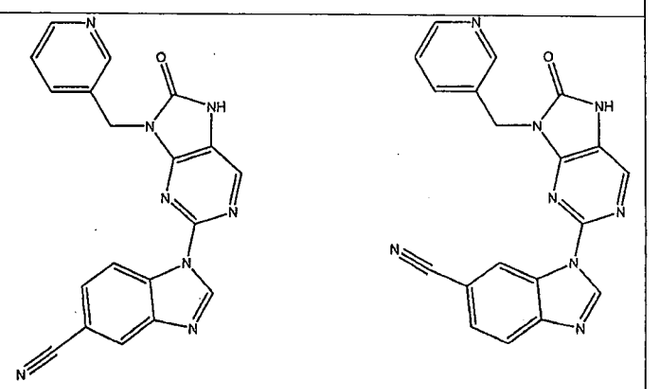
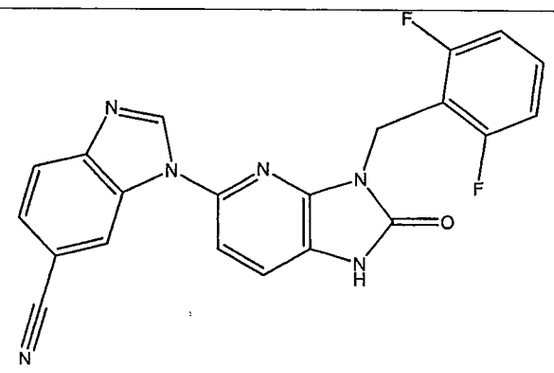
GST en el extremo 5'. Este fragmento de ADN GST-Jak3 fusionado se clonó en el sitio EcoRI del plásmido donante pFastBac 1 (Life Technologies #10359-016). La transformación, transposición y transfección de células de insecto (Sf9) se realizaron de acuerdo con las instrucciones del fabricante. El lisado de células que contenía GST-Jak3 recombinante se utilizó en el análisis de cinasa. Anticuerpo anti-GST (10 µg/ml, Sigma #G1417) se recubrió en una placa de 384 pocillos a 4 °C de un día para otro. Lisado de células que contenía GST-Jak3 (dilución 1:100) se agregó a las placas recubiertas con anti-GST, y se capturó GST- Jak3 mediante anticuerpo anti-GST inmovilizado. Los compuestos de prueba y la mezcla de sustrato (50 mM HEPES, pH 7, 0.5 mM Na_3VO_4, 25 mM $MgCl_2$, 1 mM DTT, 0.005% BSA, 1 µM ATP, y 4.5 µg/ml poly-Glu, Ala, Tyr biotinilada) se agregaron a la placa para iniciar la reacción. Luego de una incubación de 60 minutos, la reacción se detuvo con 4 mM EDTA, y la fosforilación de poly-Glu, Ala, Tyr biotinilada se detectó usando 17 µg/ml Cy5-estreptavidina (Amersham, #PA92005) y 2.7 µg/ml de anticuerpo anti-fosfotirosina conjugado con europio (PerkinElmer #AD0069) usando tecnología de fluorescencia homogénea con resolución de tiempo (HTRF).

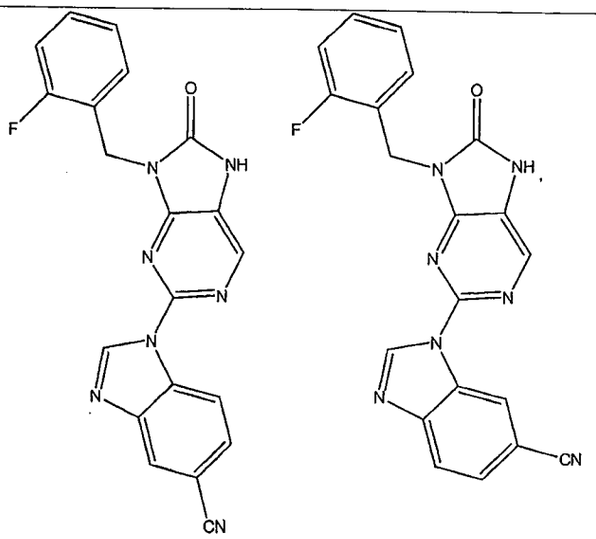
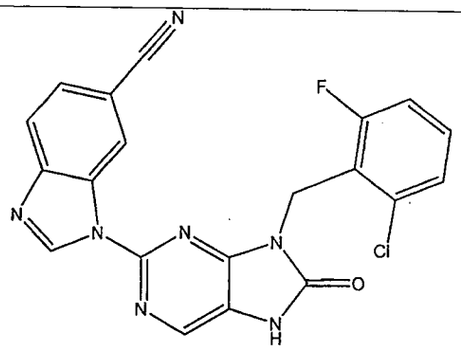
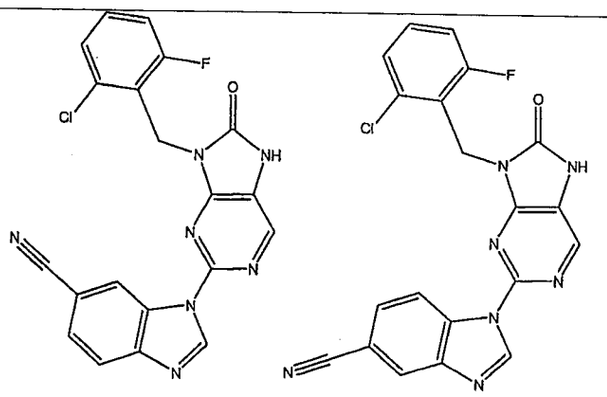
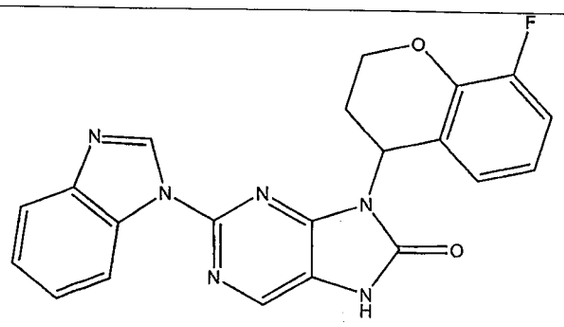
Análisis celular Jak3

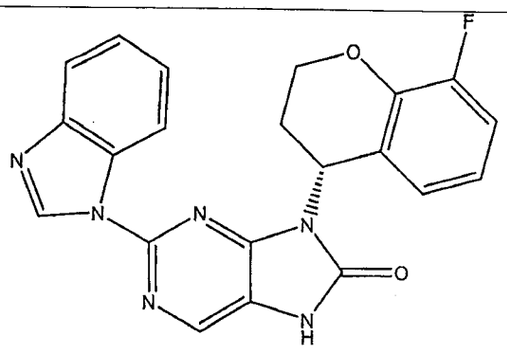
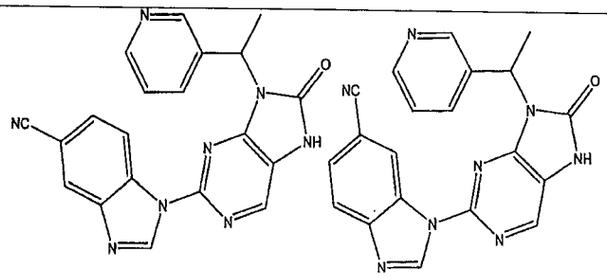
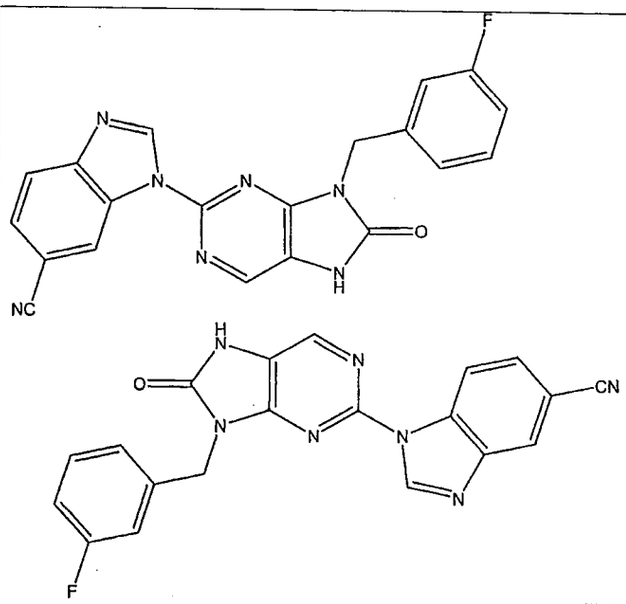
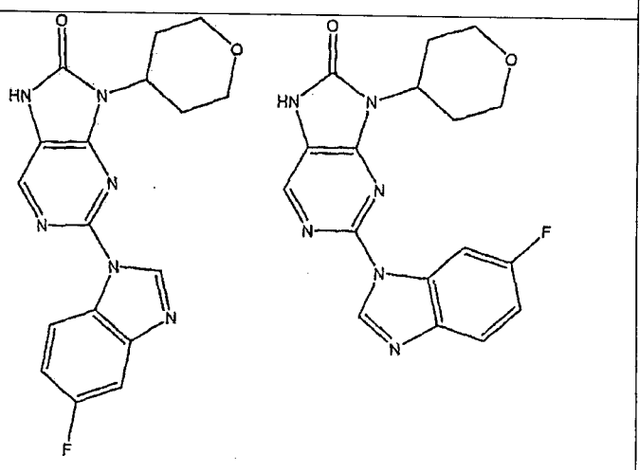
[00396] La línea de células linfocito pre-B F7 de ratón se utilizó para el análisis de Jak3 celular. ADNc de IL-2Rβc humano se expresa establemente en células F7 (Kawahara et al., 1995). Células F7 se mantuvieron en medio RPMI 1640 suplementado con 10% de suero fetal bovino más IL-3. Células (30.000 células/pocillo) en medio libre de suero se sembraron en placas de 96 pocillos para el análisis de proliferación celular. Compuestos de prueba se agregaron a las células, seguidos por la adición de IL-2 (final 20 ng/ml). Luego de 24 horas de incubación, se determinó el número de células viables mediante el kit CellTiter-Glo Luminescent Cell Viability Assay (Promega, #G7573) de acuerdo con las instrucciones del fabricante.

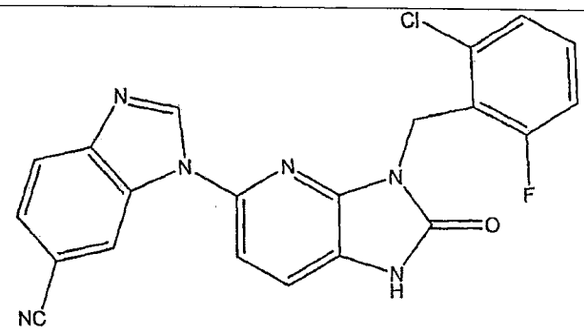
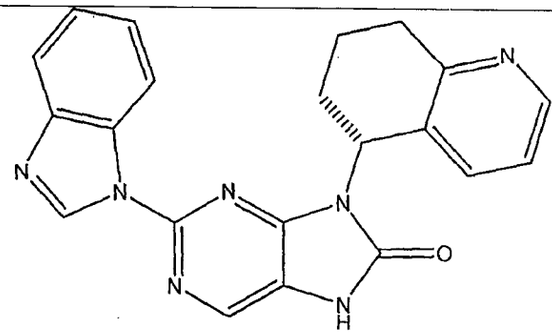
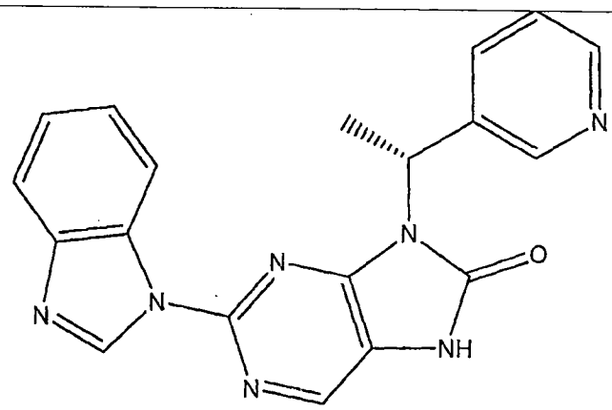
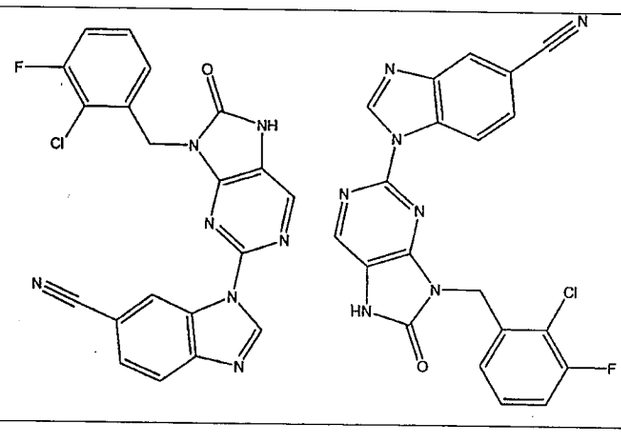
[00397] Los resultados de las pruebas de especies representativas se muestran a continuación. Los compuestos en Tabla 1 exhibieron una IC_{50} menor de 100nM. Los compuestos en Tabla 2 exhibieron una IC_{50} entre 101 nM y 1μM. Los compuestos en la Tabla 3 exhibieron una IC_{50} entre 1μM y 10μM.

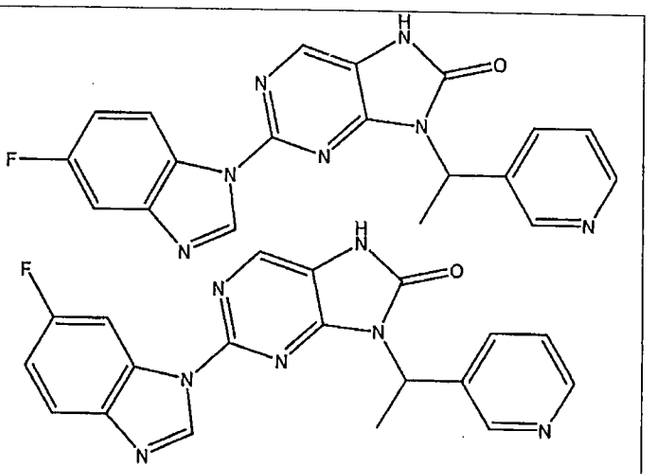
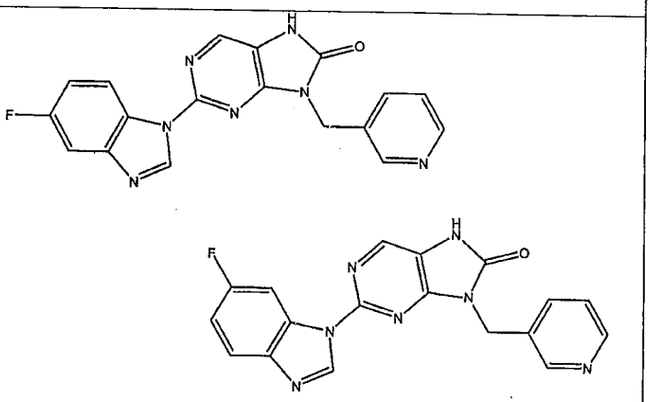
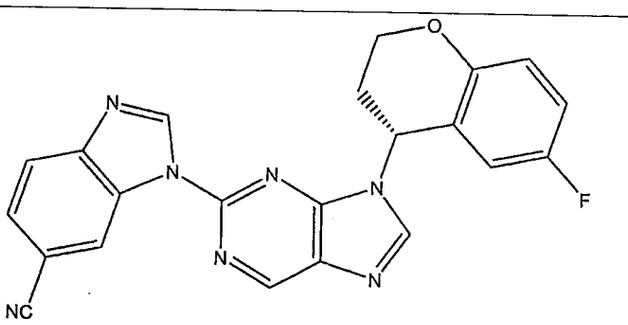
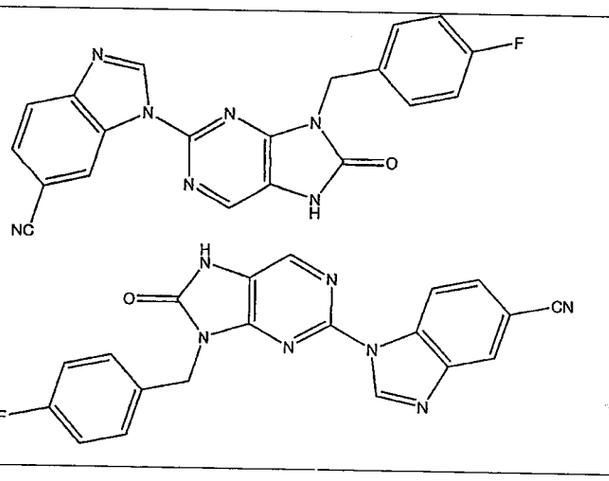
Ejemplo de Síntesis	Referencia No.	TABLA 1
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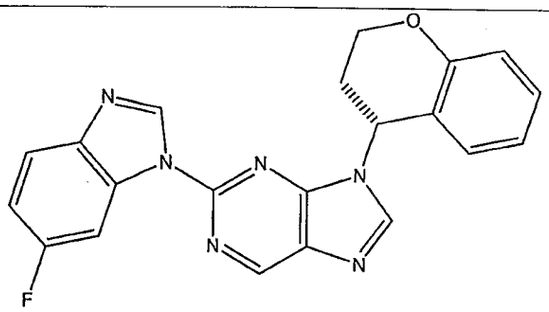
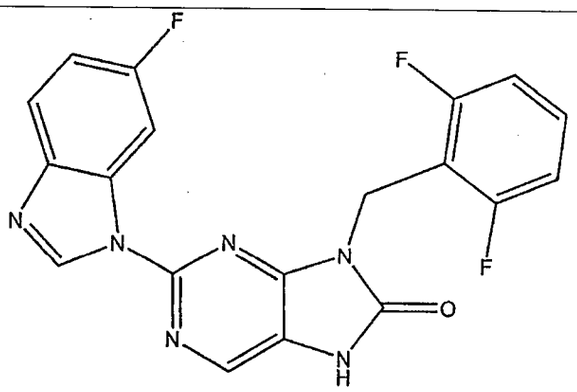
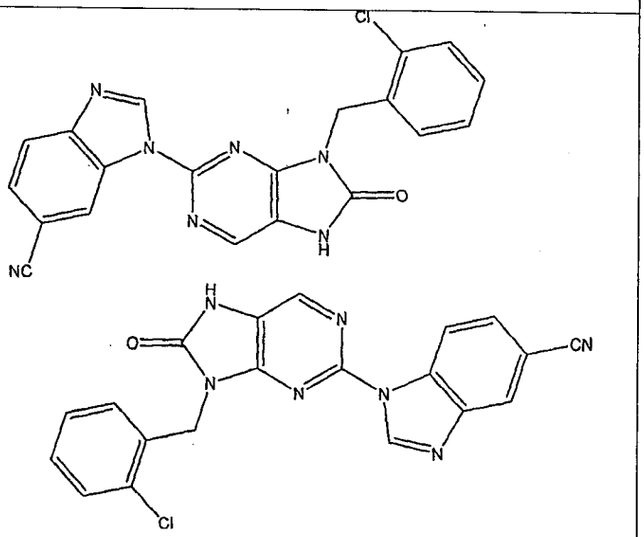
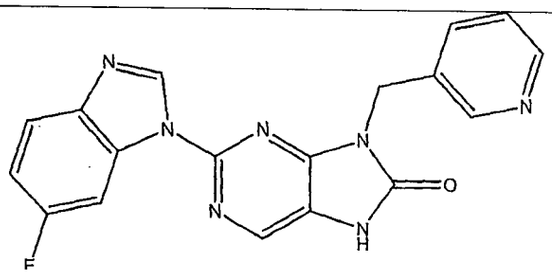
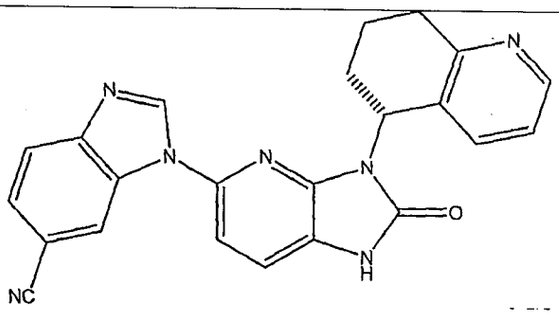
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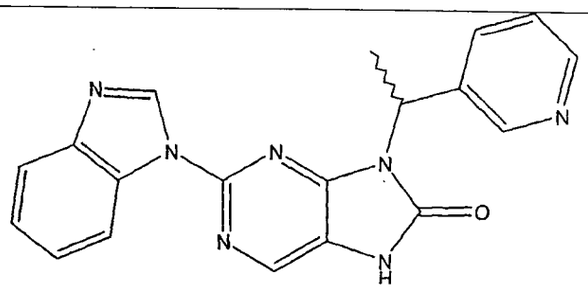
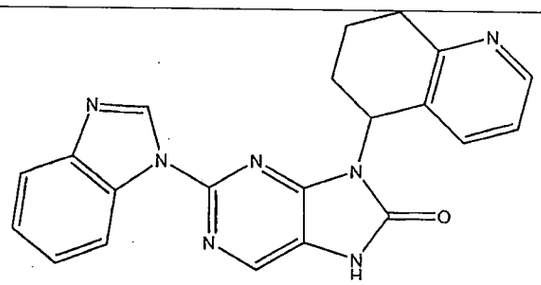
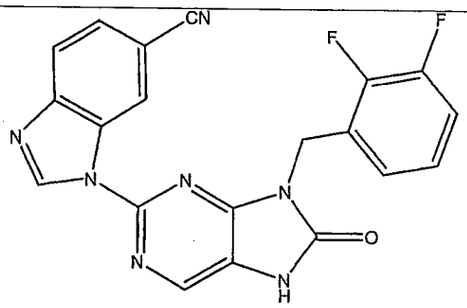
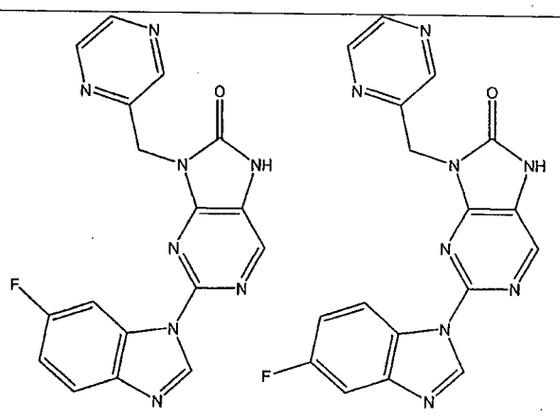
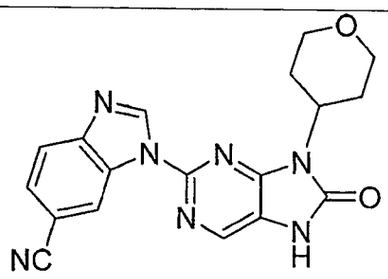
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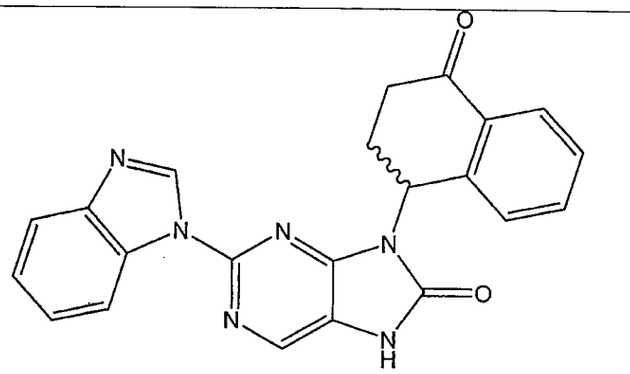
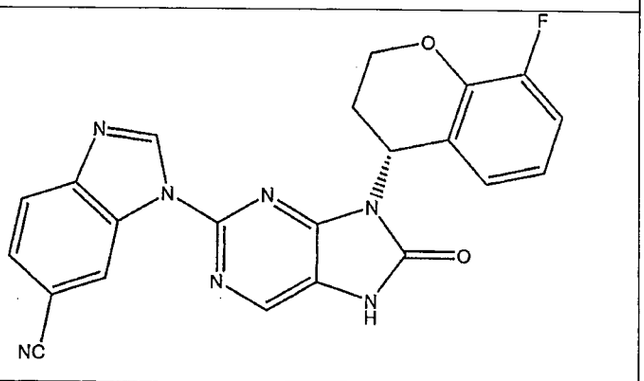
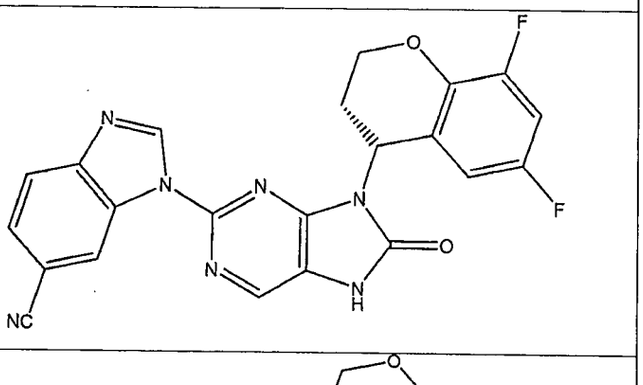
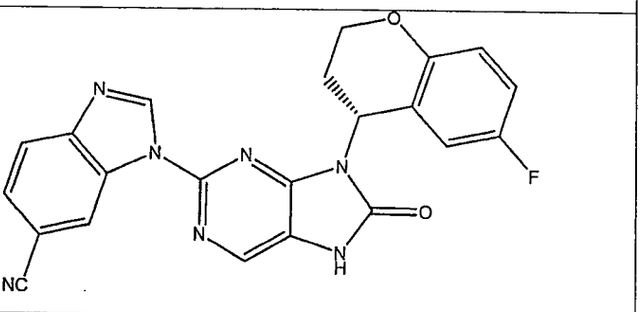
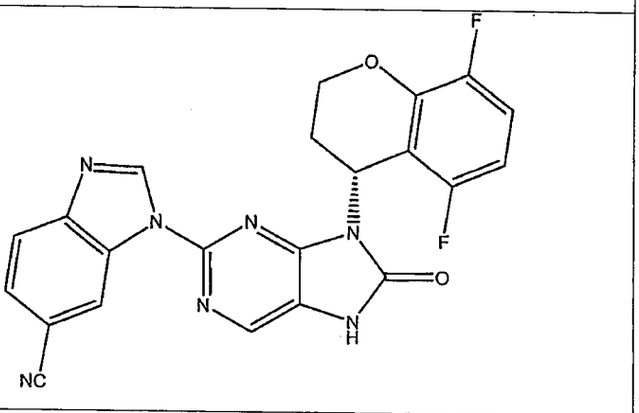
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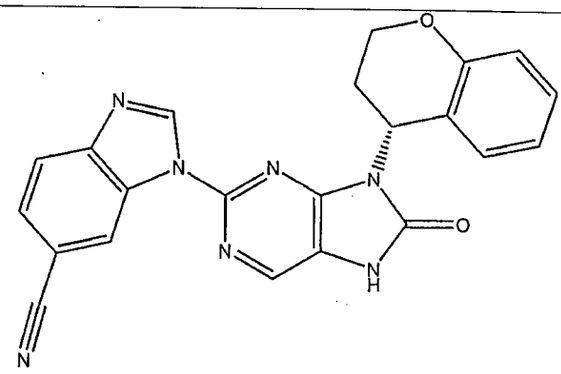
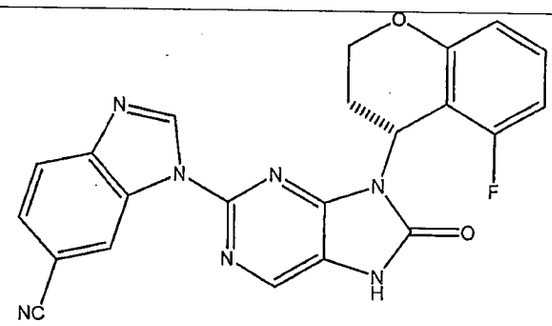
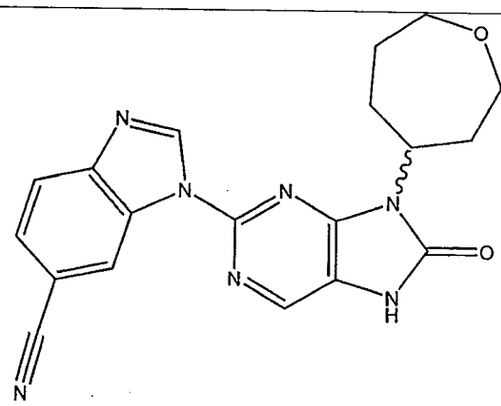
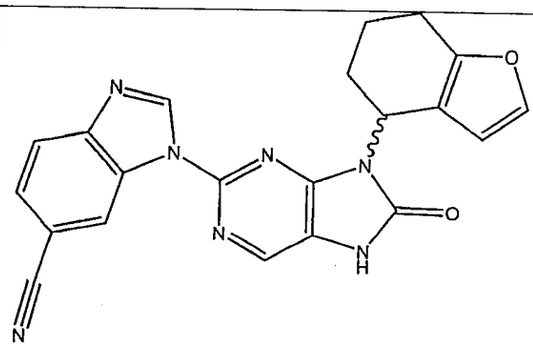
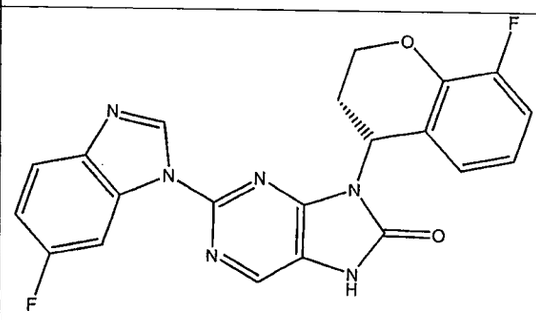
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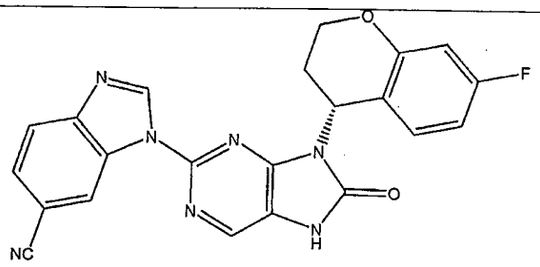
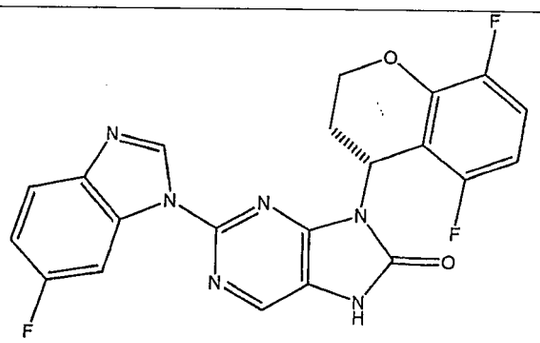
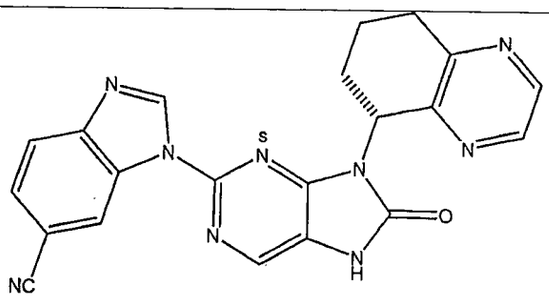
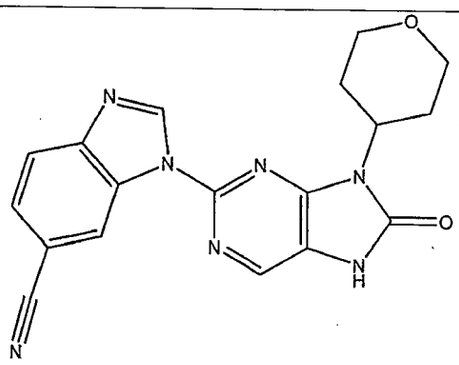
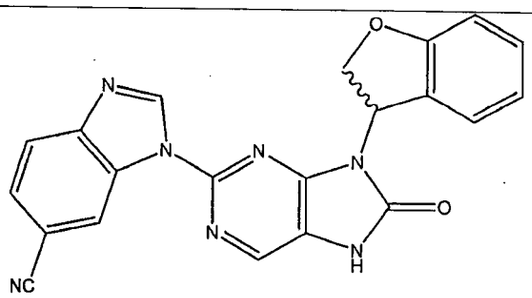
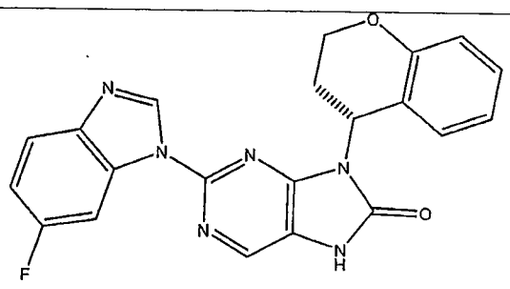
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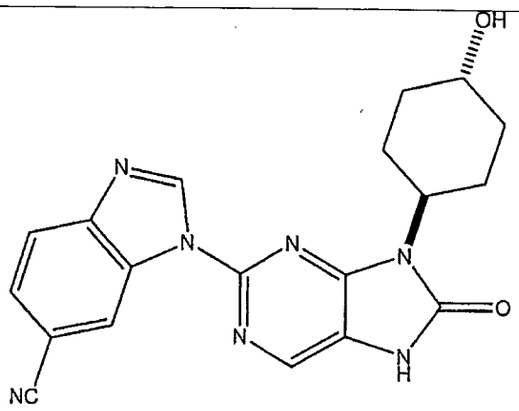
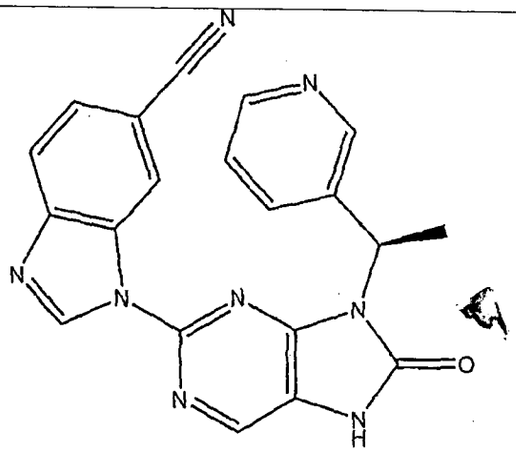
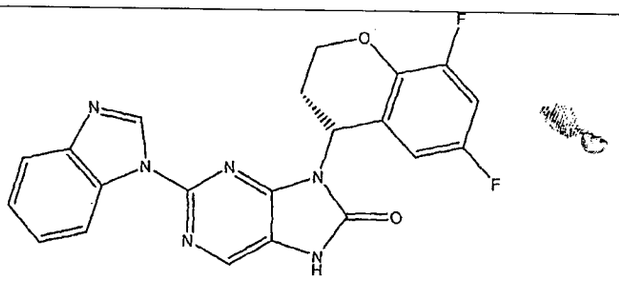
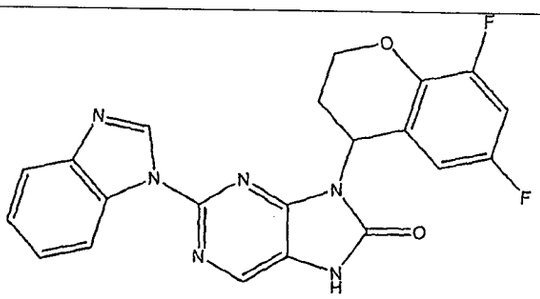
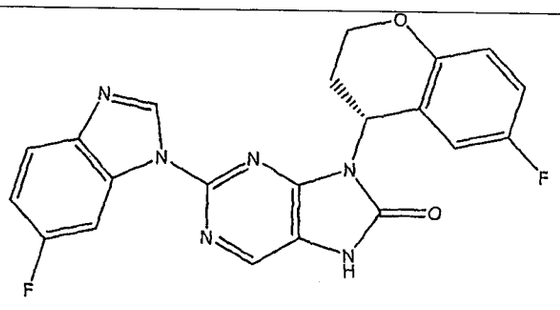
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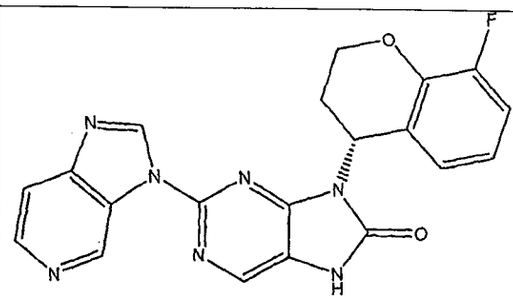
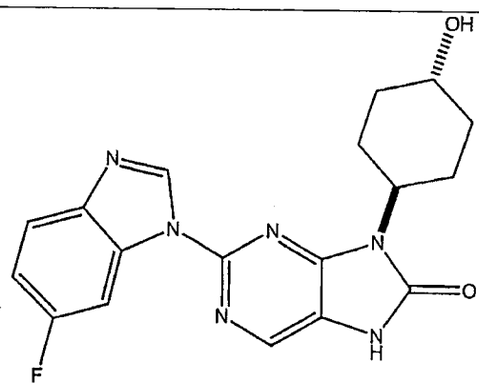
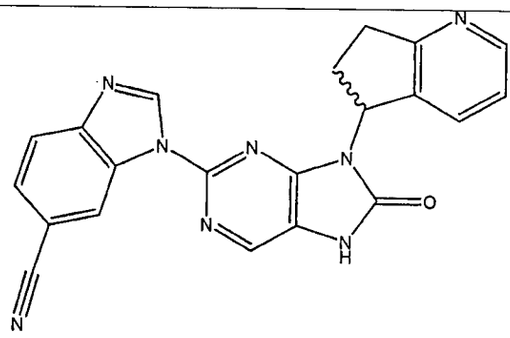
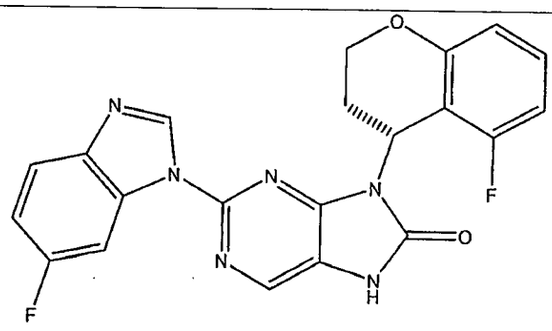
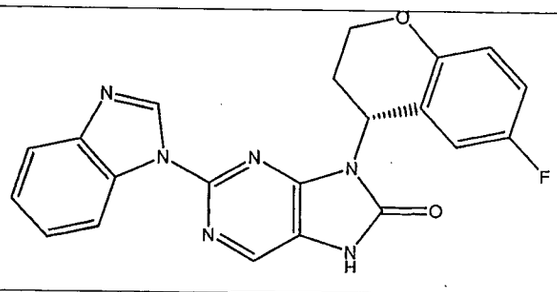
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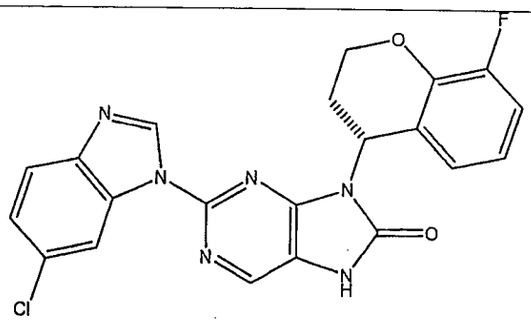
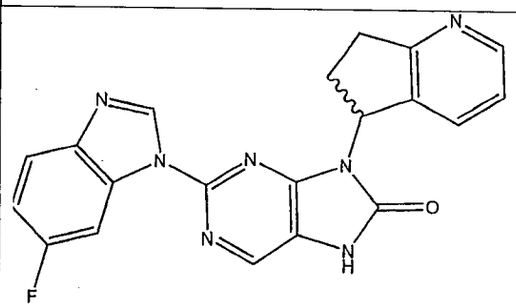
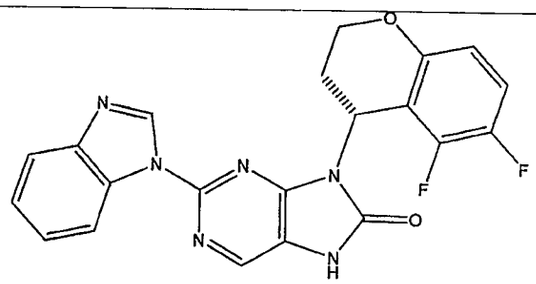
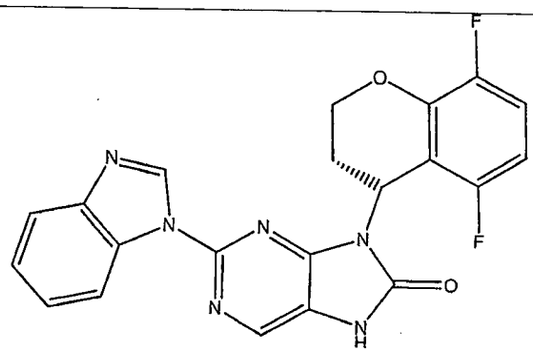
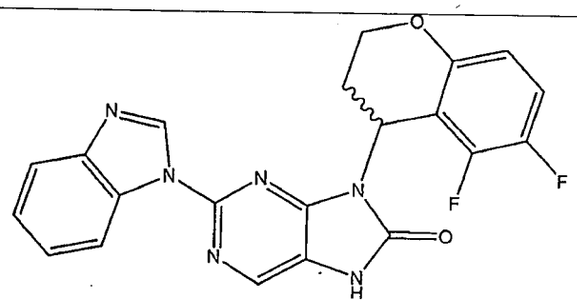
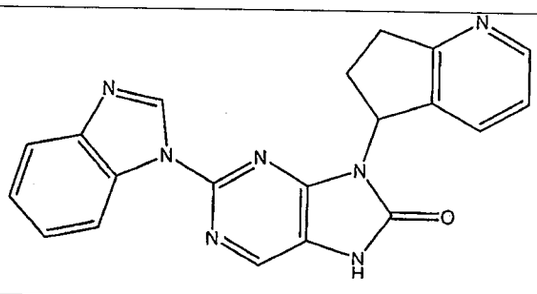
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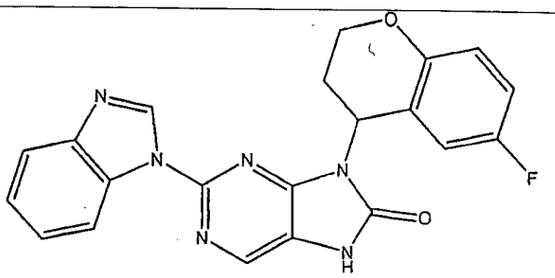
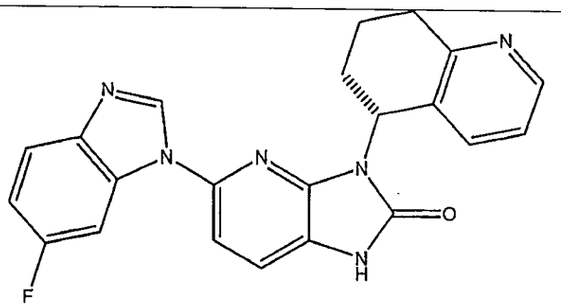
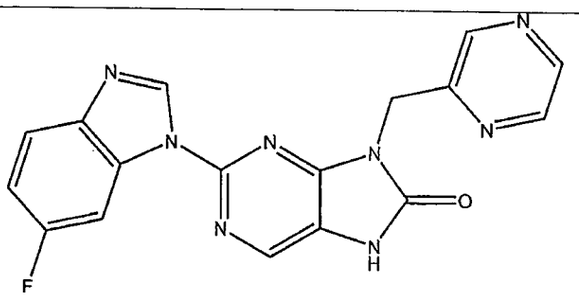
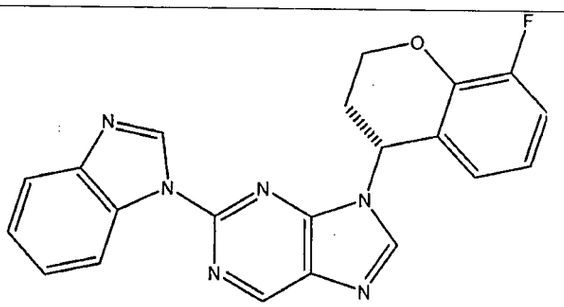
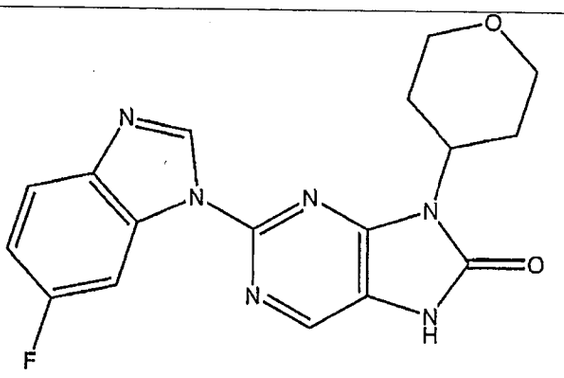
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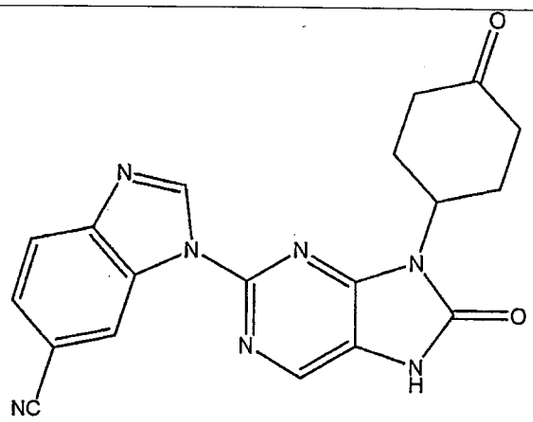
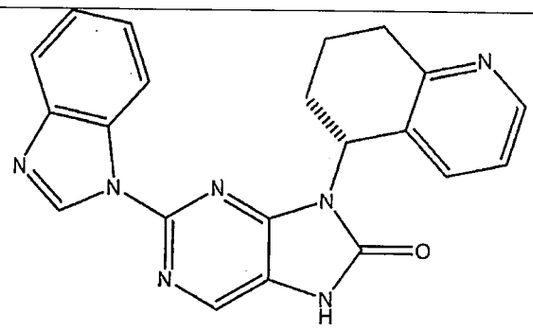
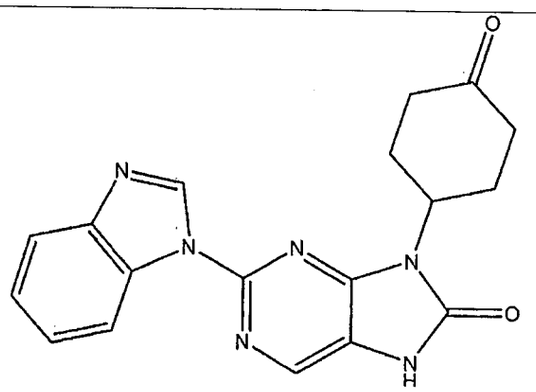
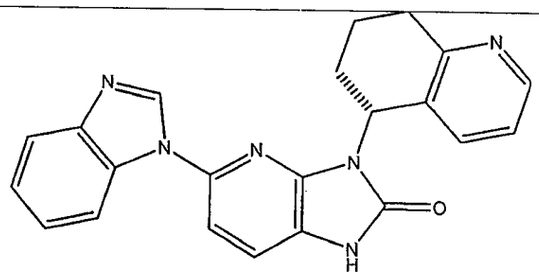
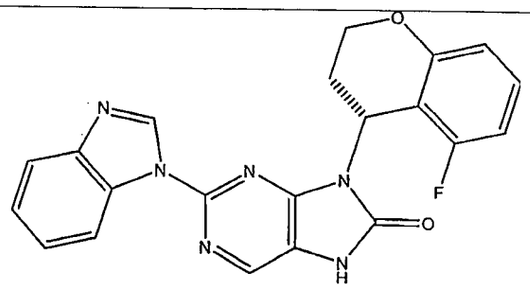
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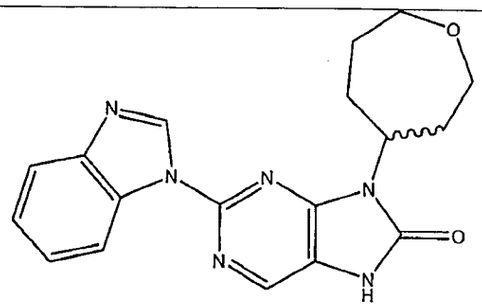
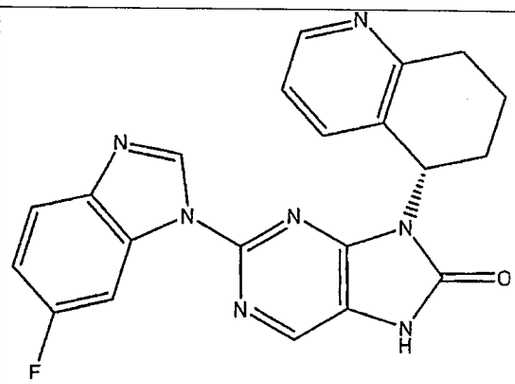
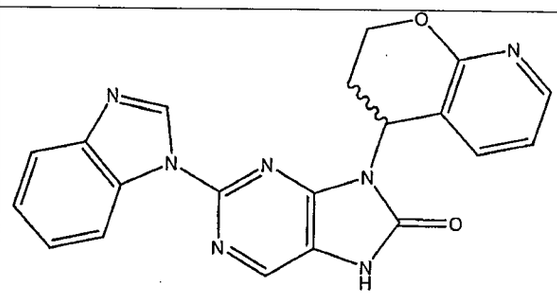
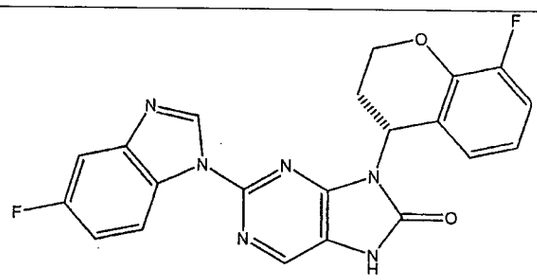
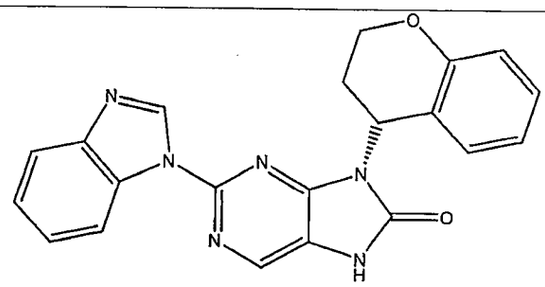
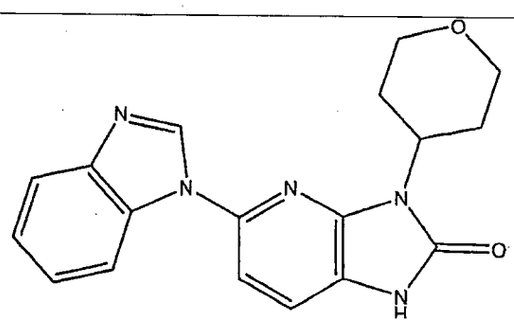
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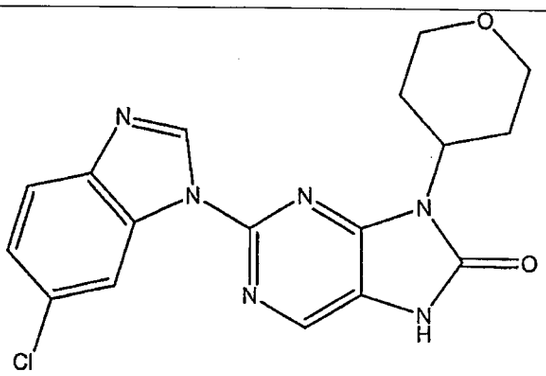
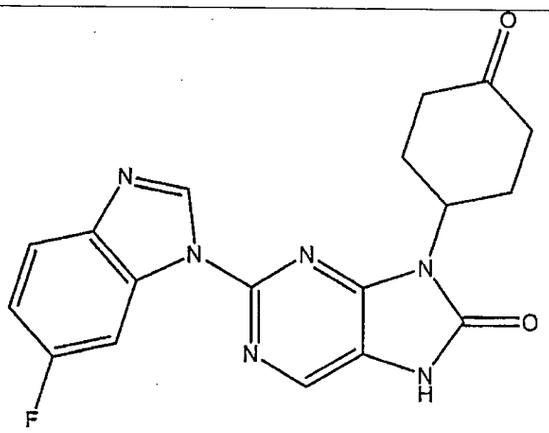
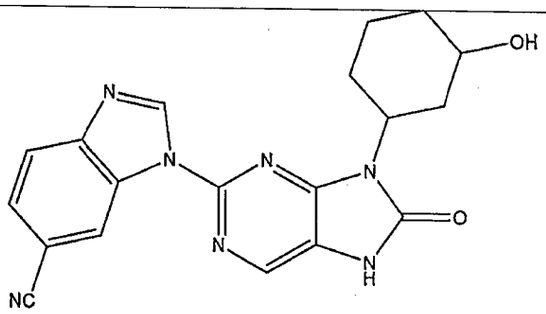
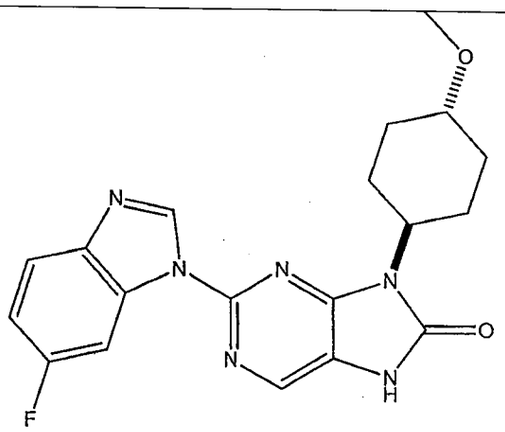
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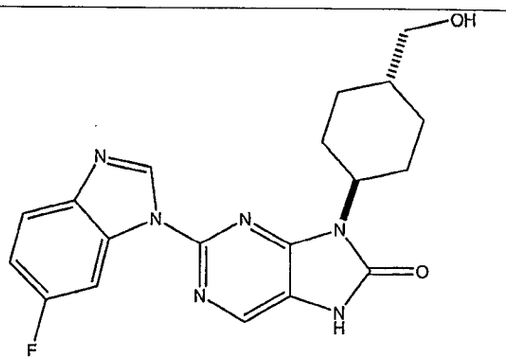
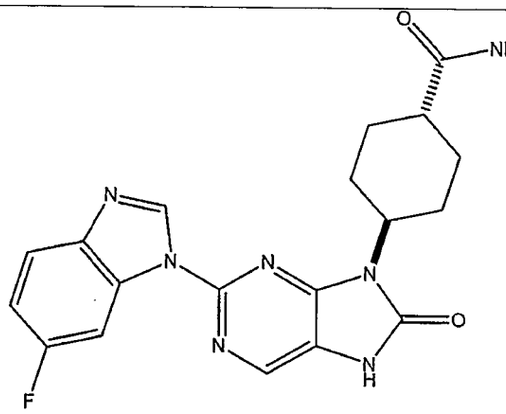
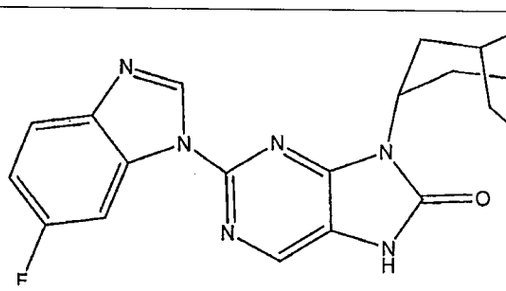
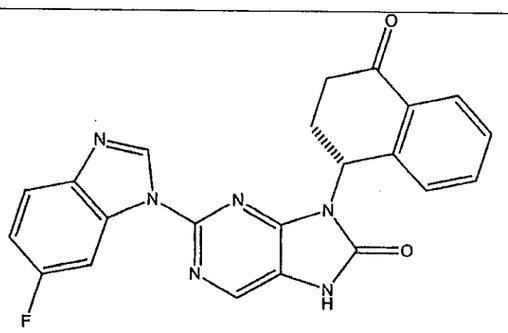
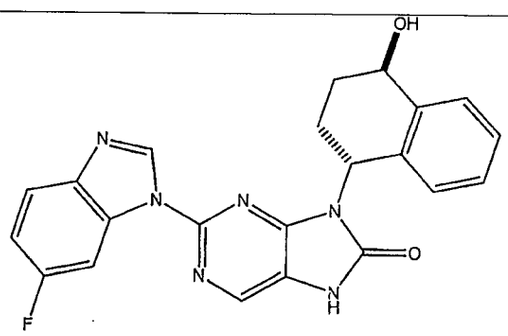
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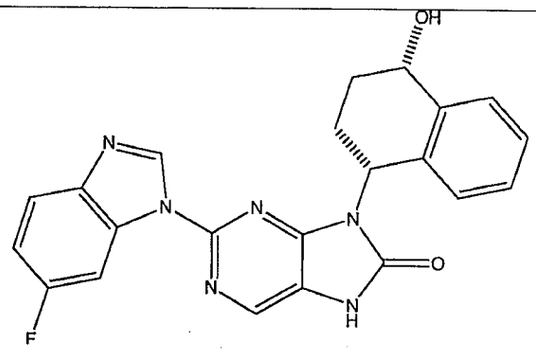
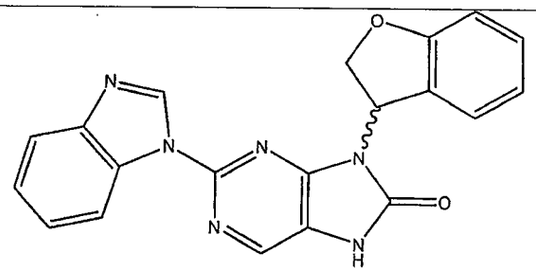
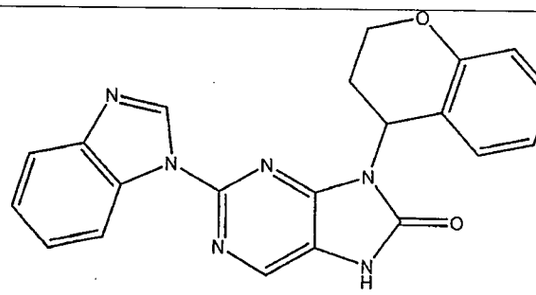
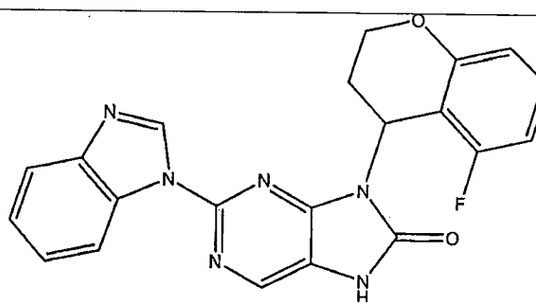
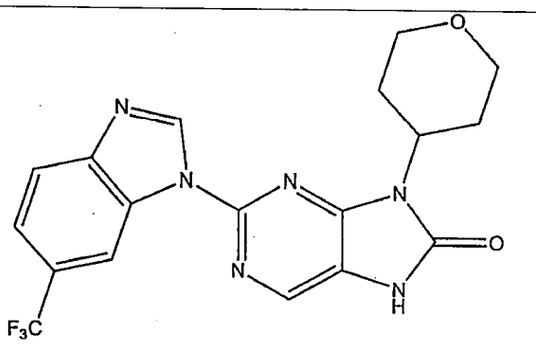
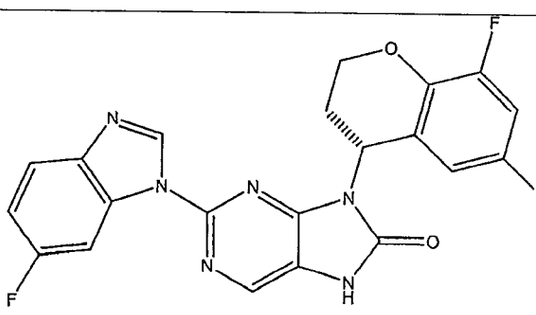
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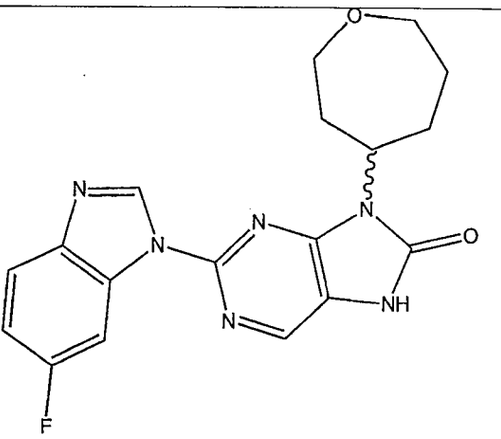
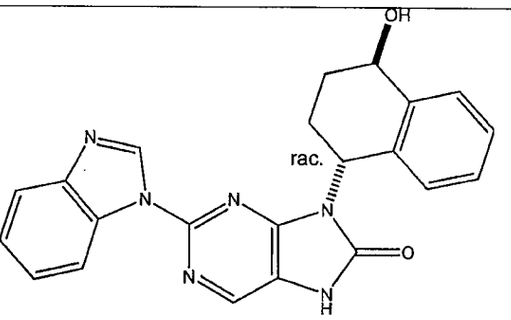
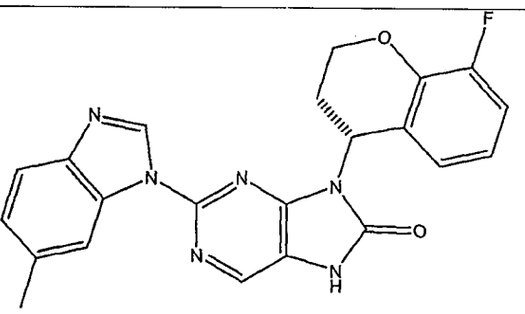
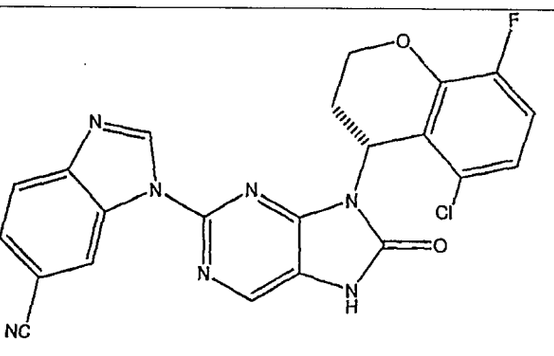
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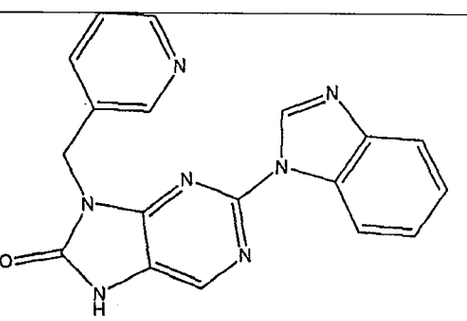
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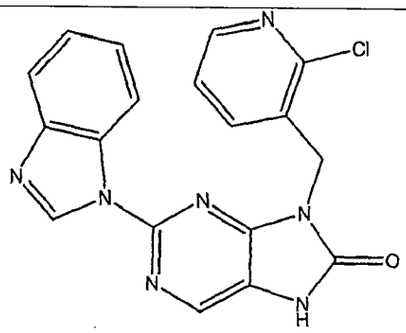
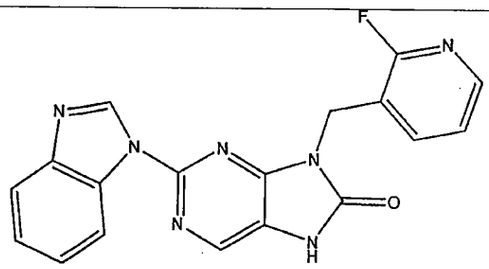
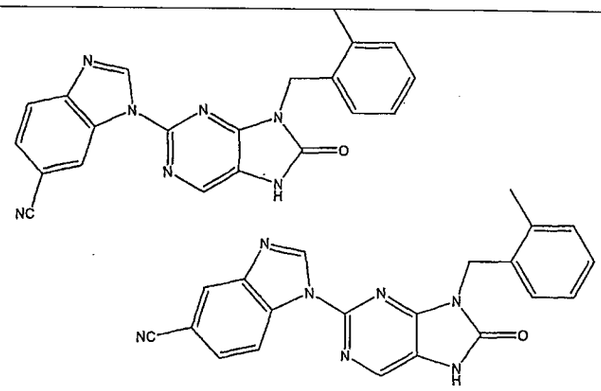
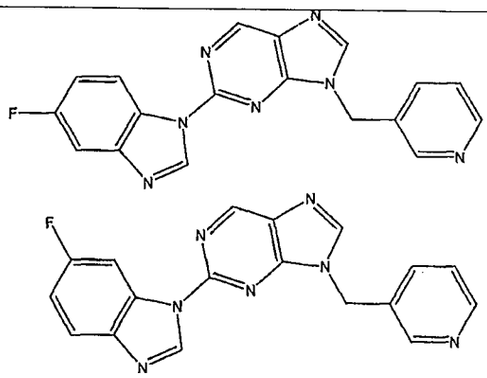
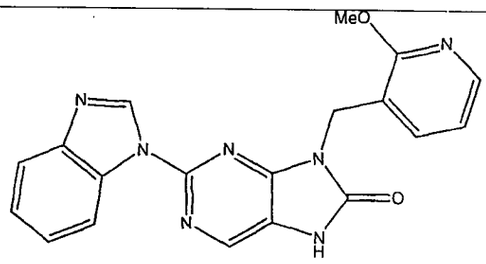
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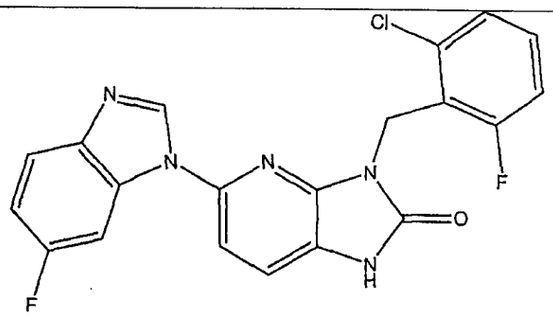
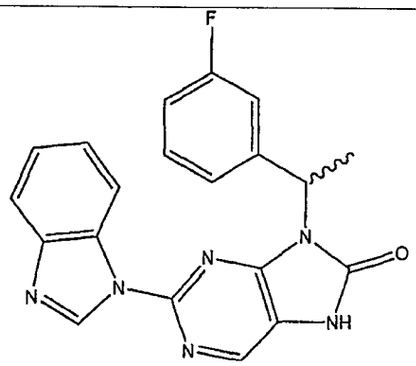
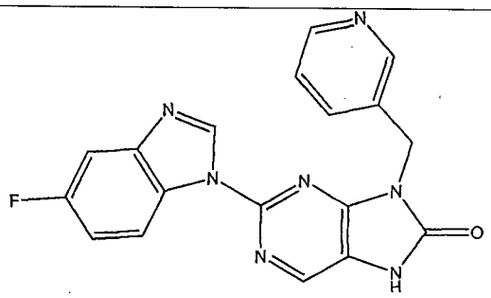
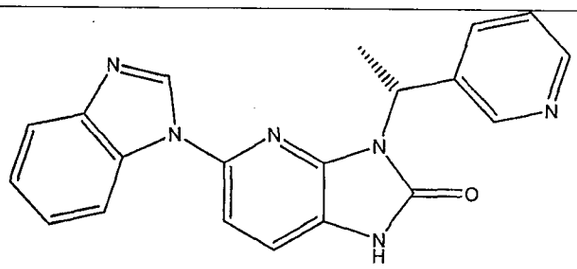
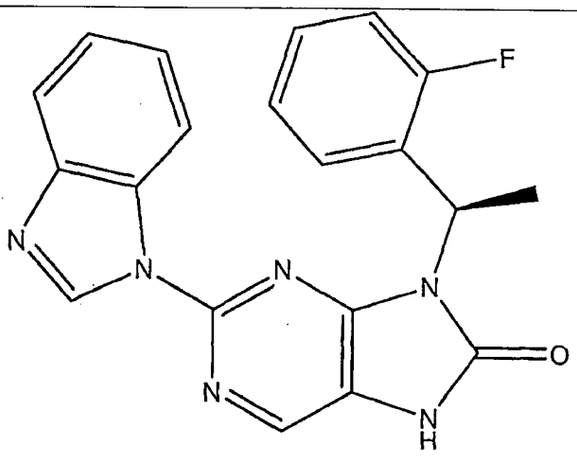
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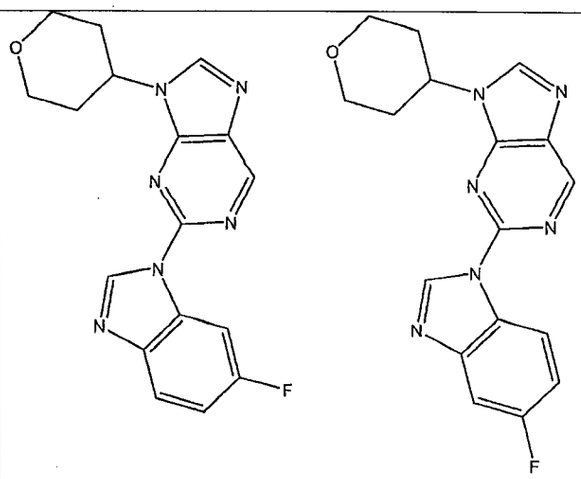
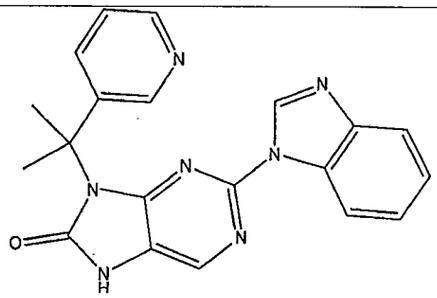
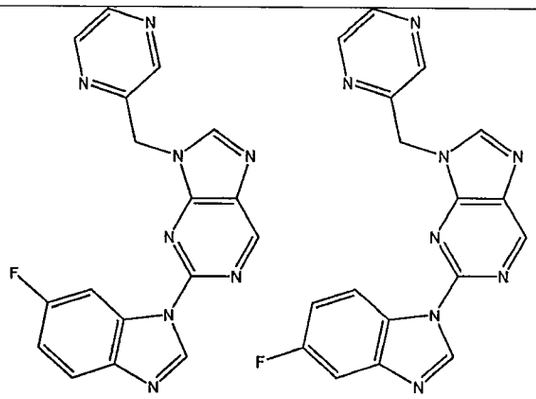
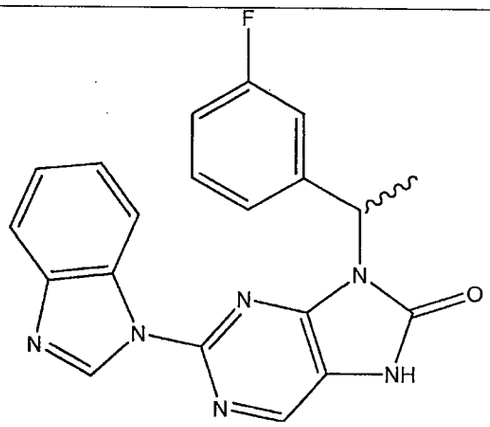
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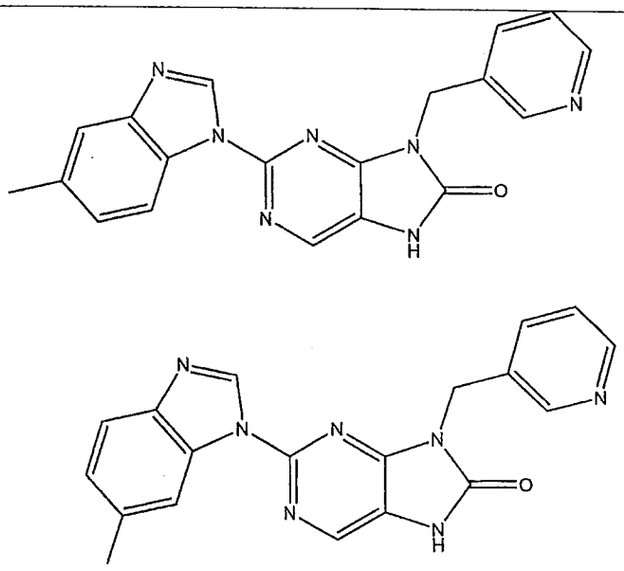
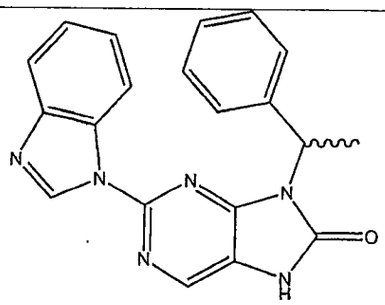
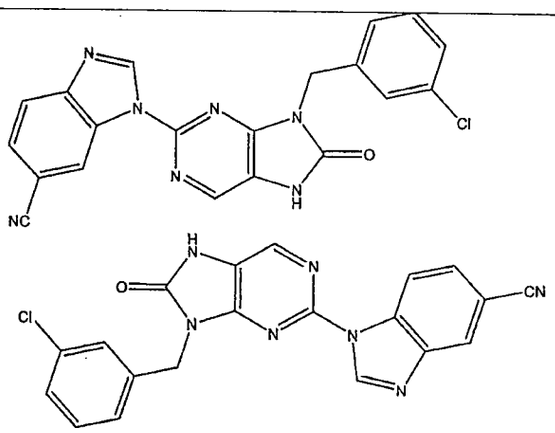
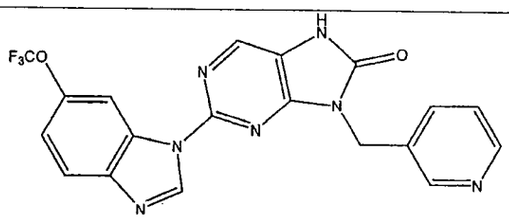
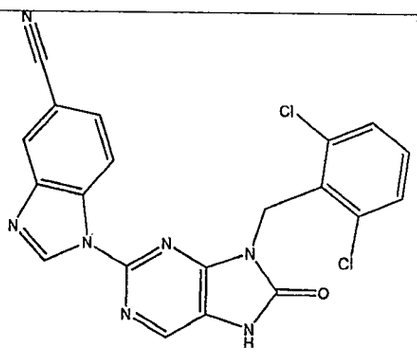
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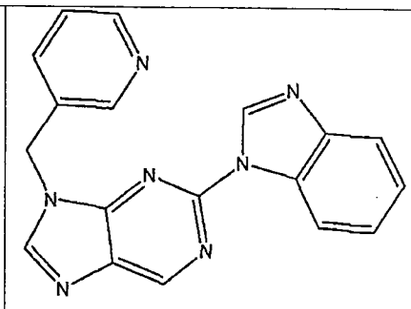
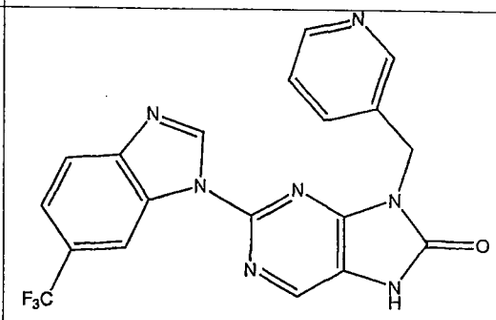
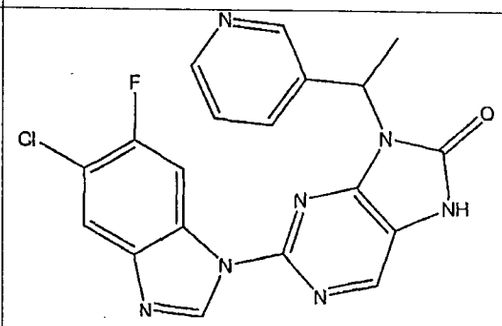
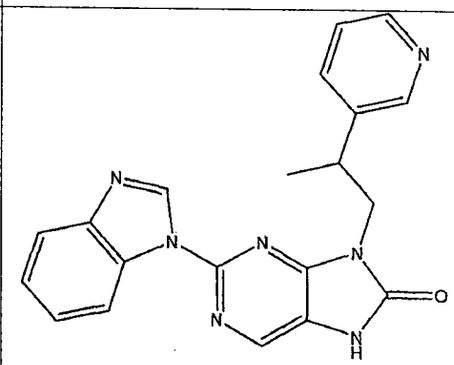
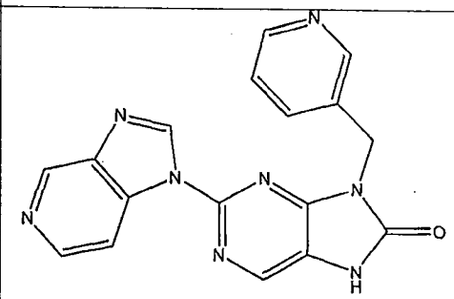
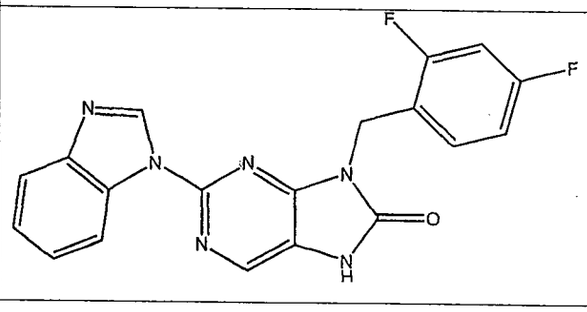
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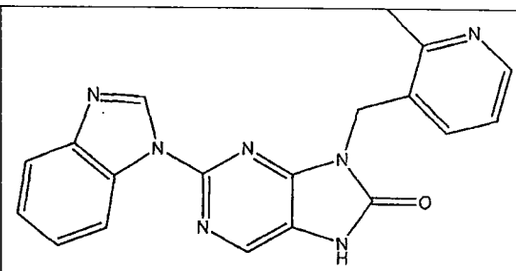
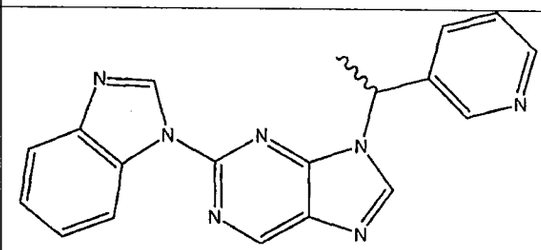
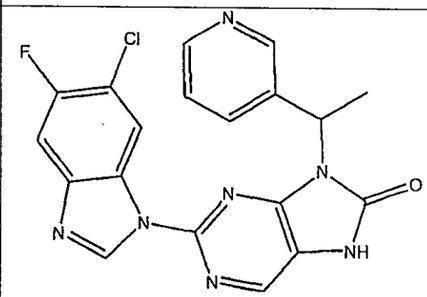
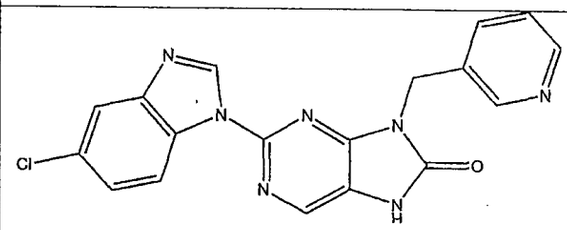
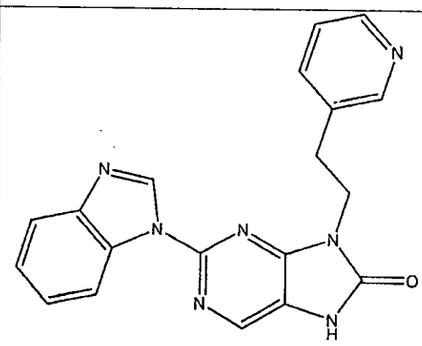
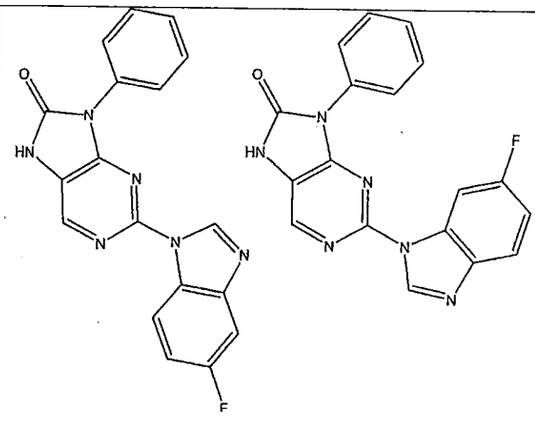
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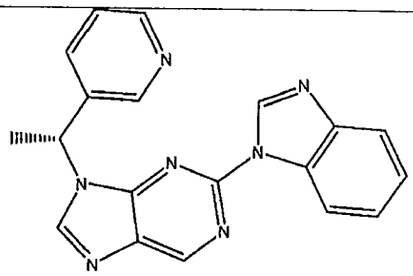
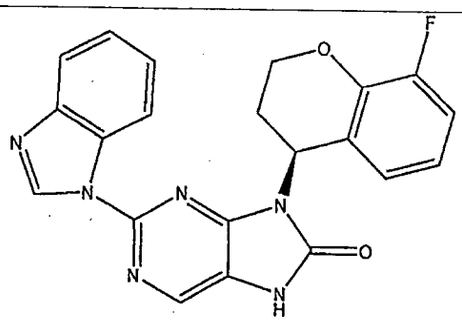
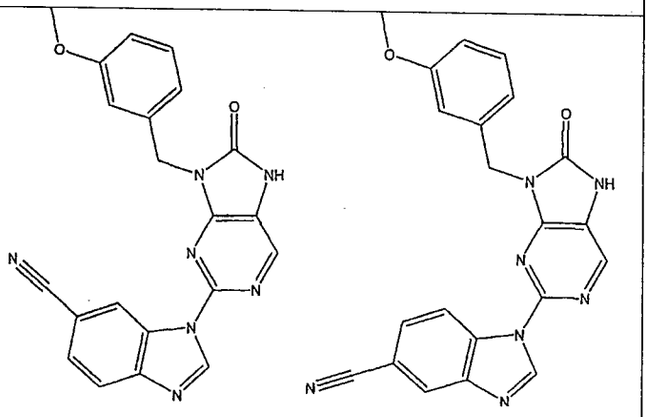
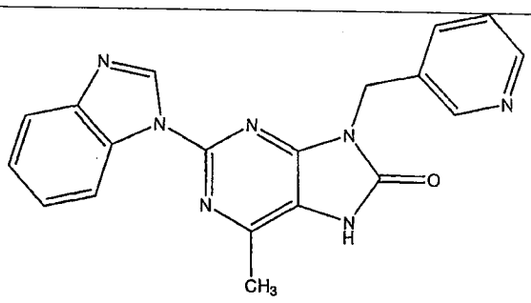
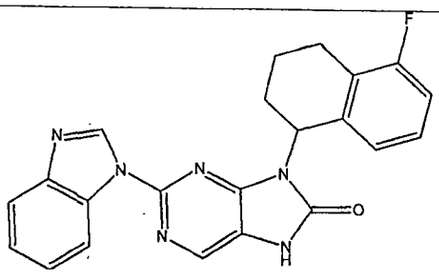
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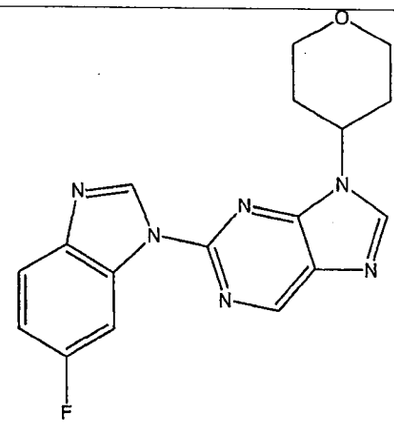
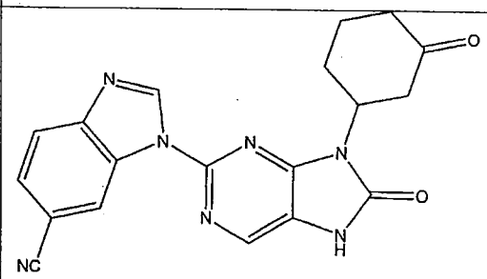
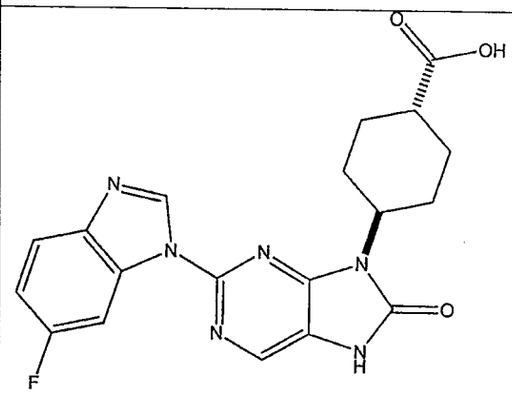
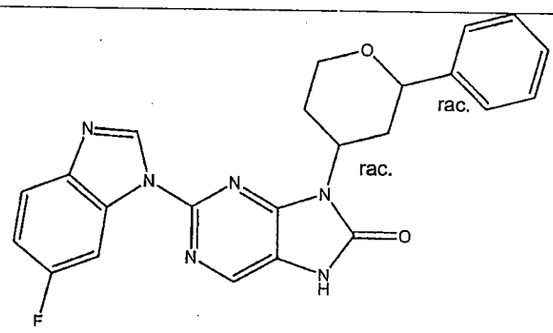
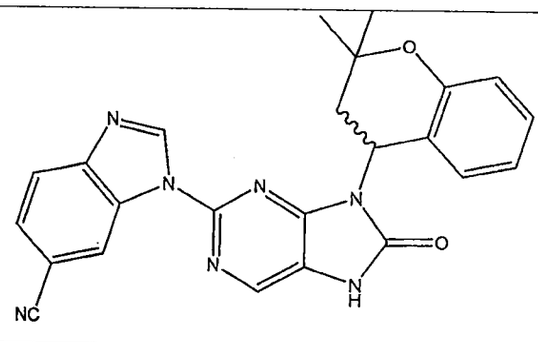
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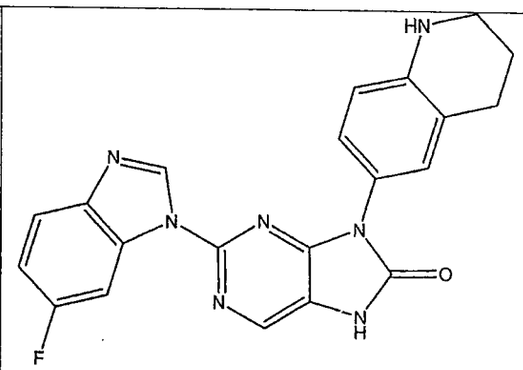
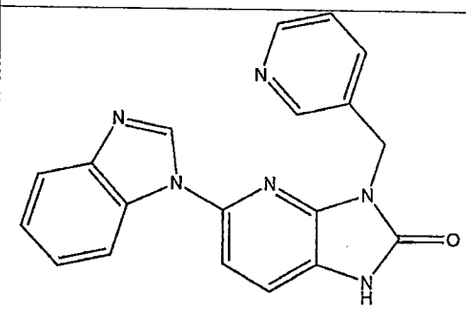
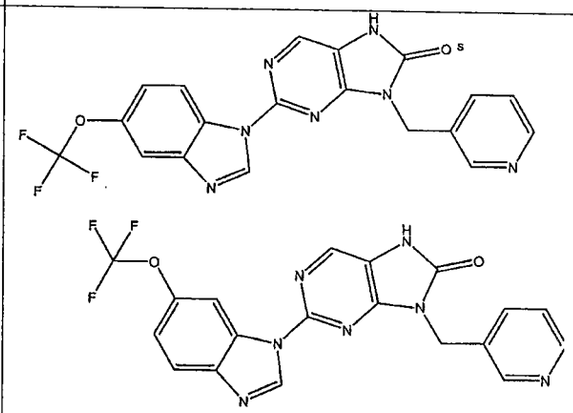
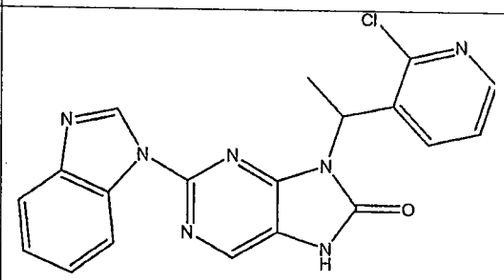
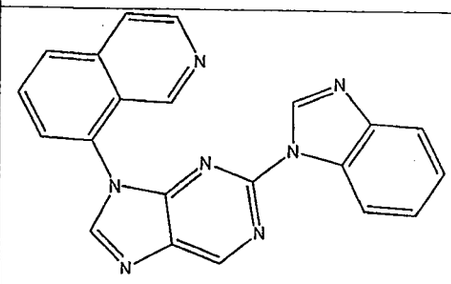
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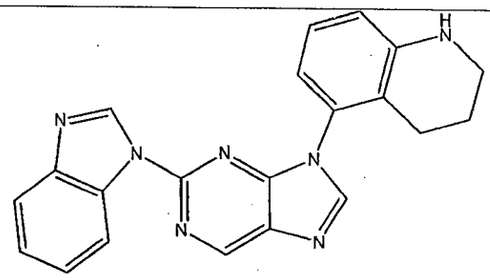
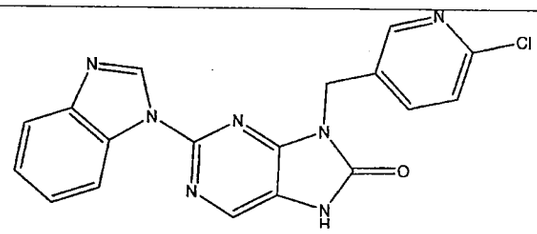
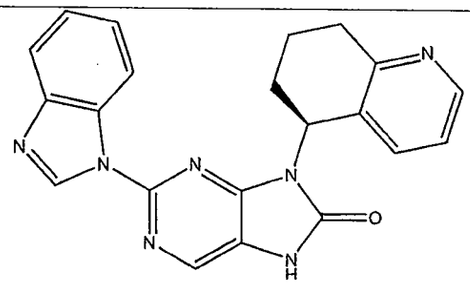
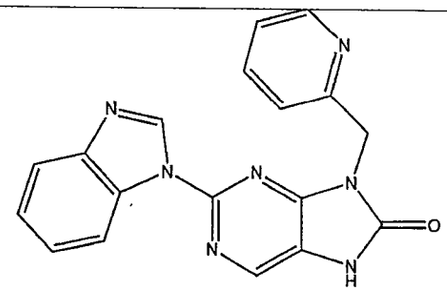
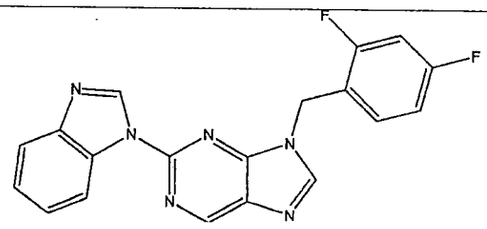
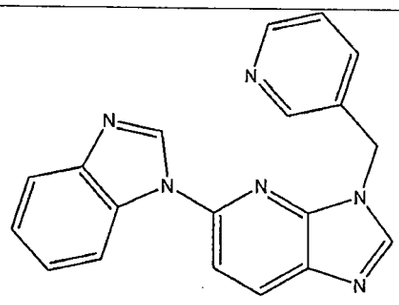
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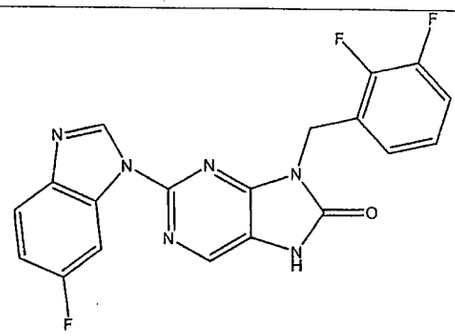
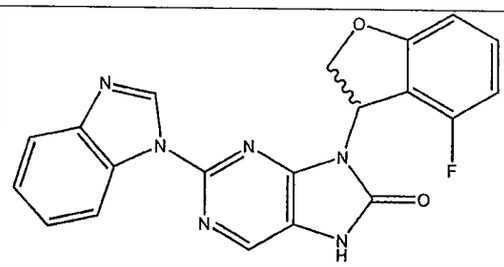
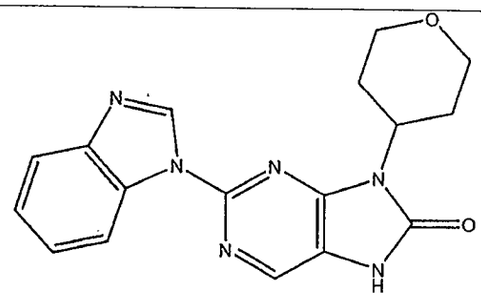
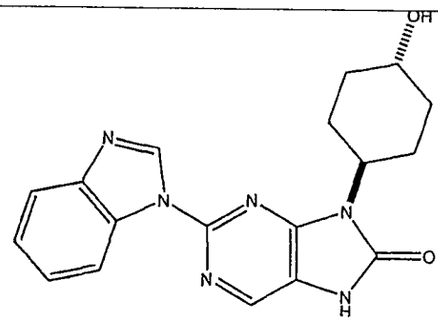
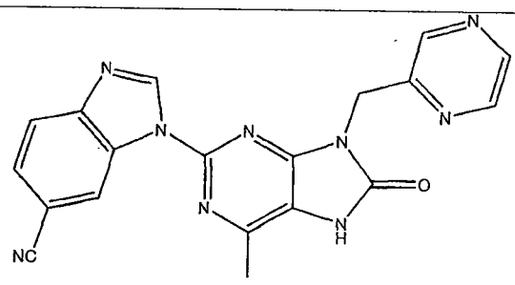
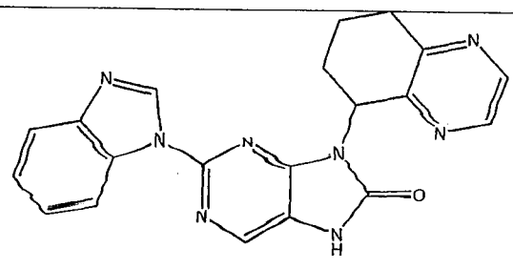
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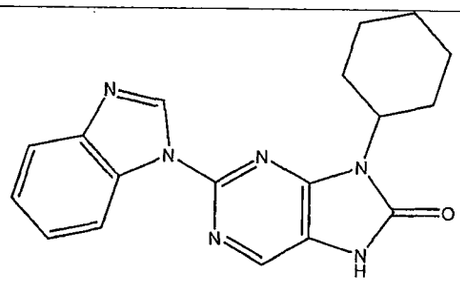
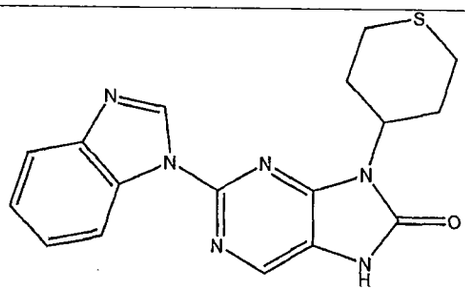
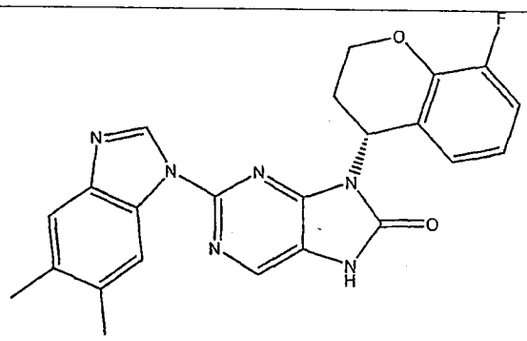
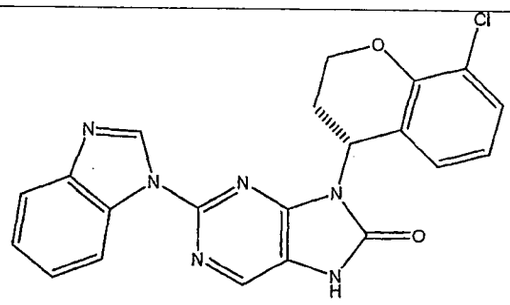
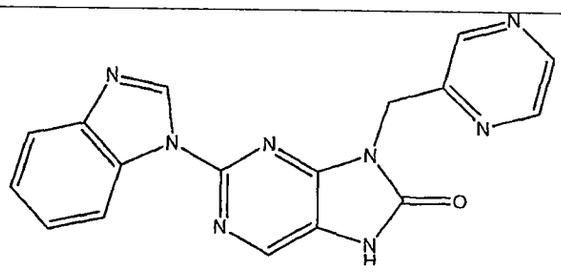
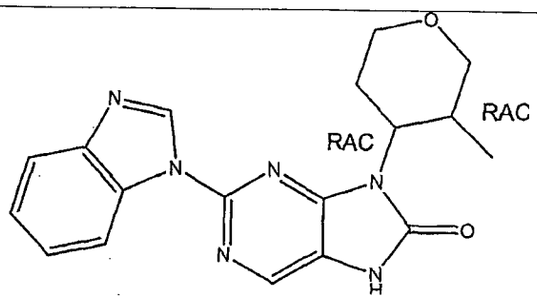
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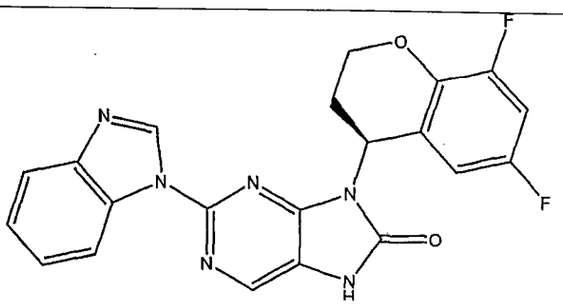
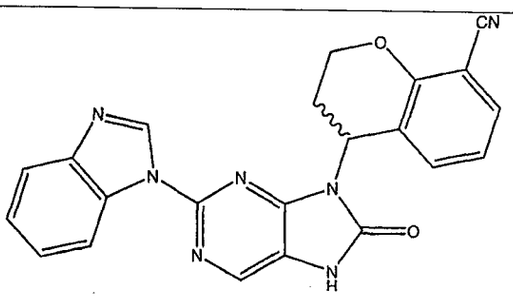
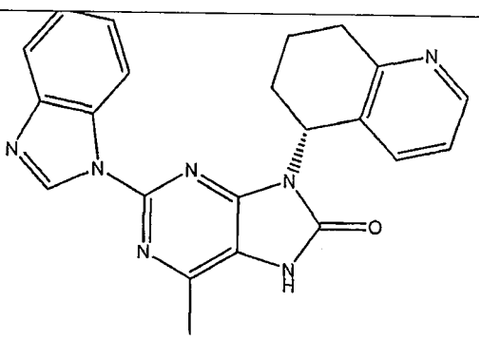
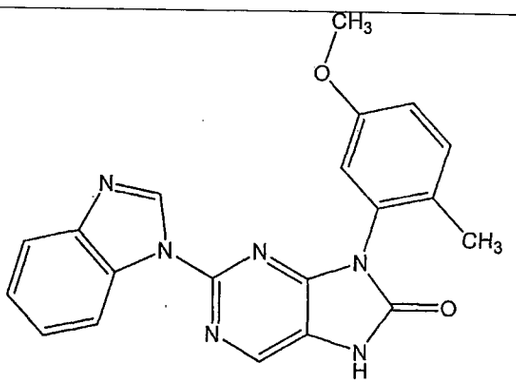
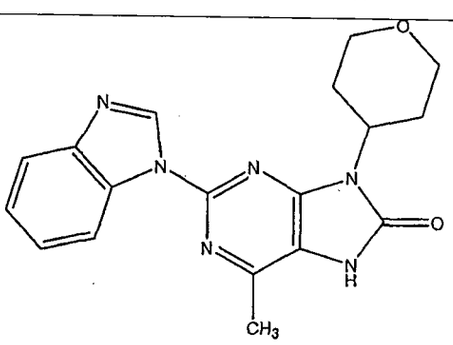
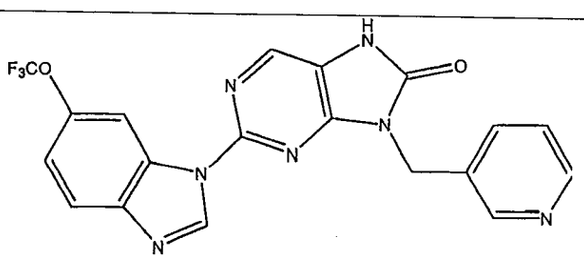
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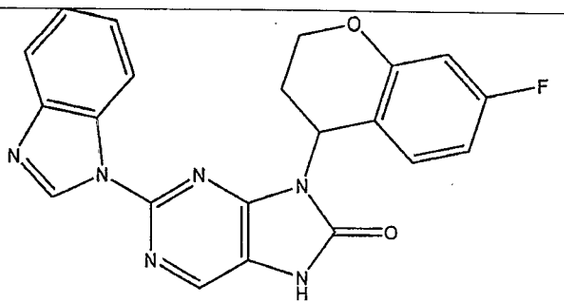
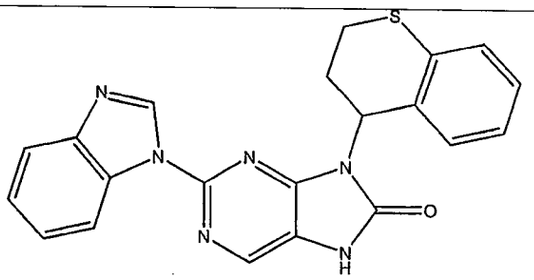
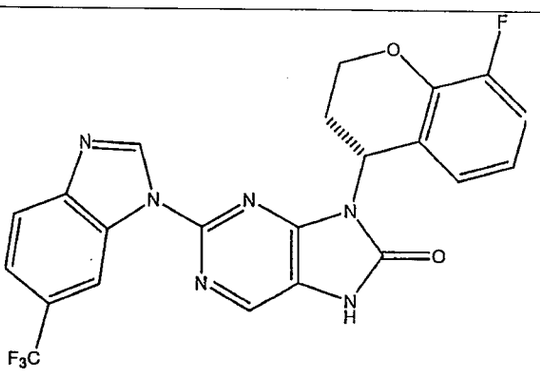
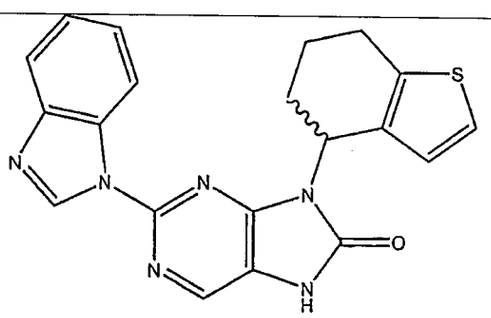
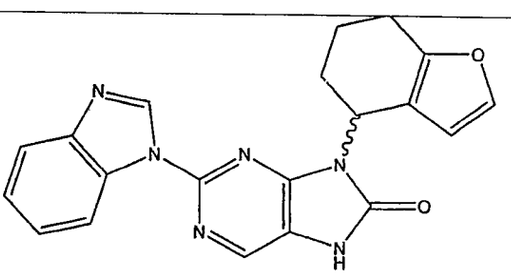
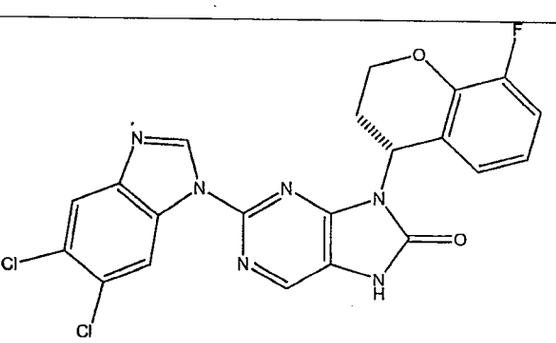
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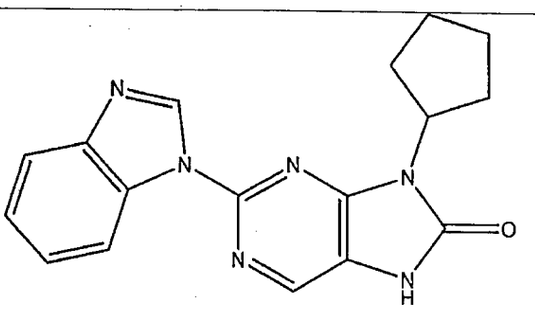
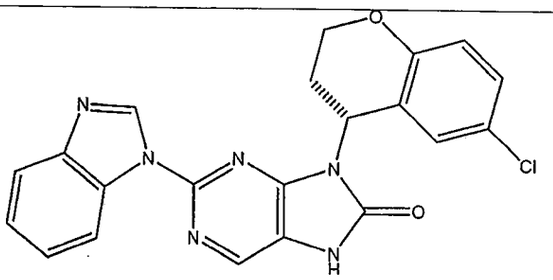
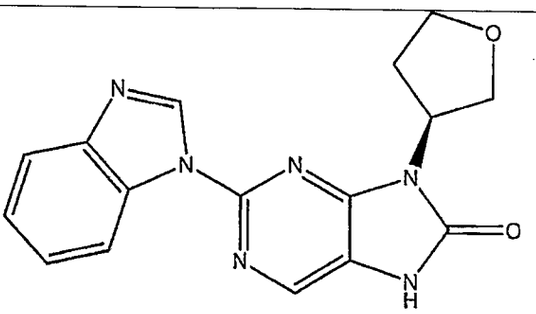
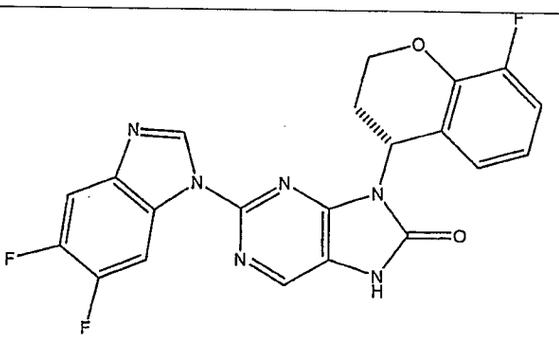
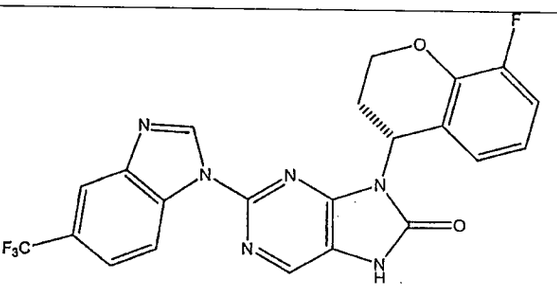
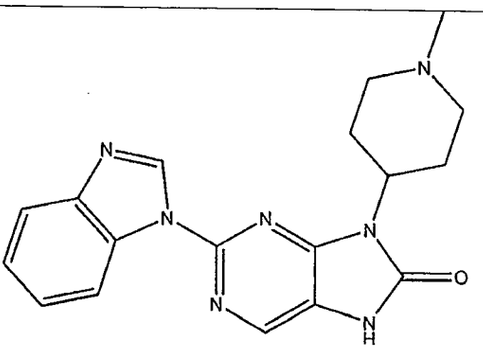
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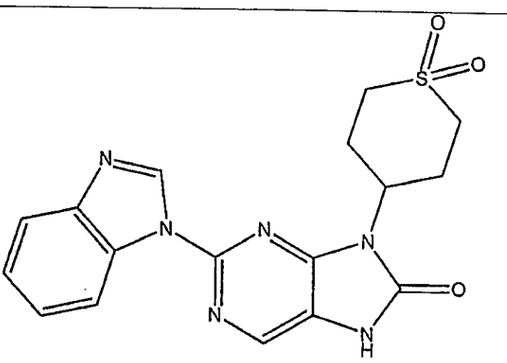
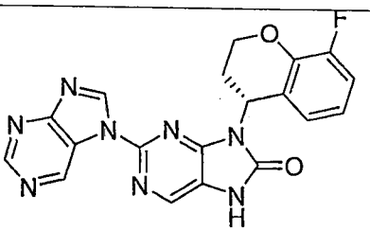
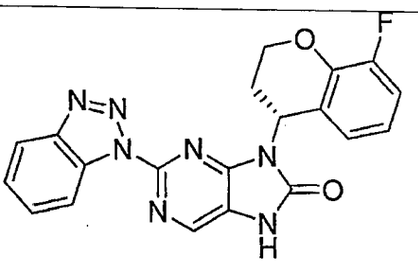
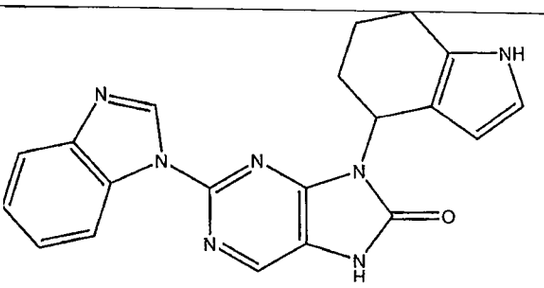
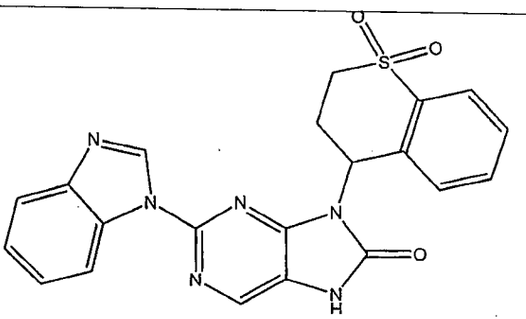
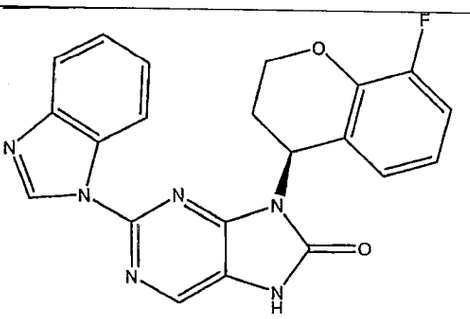
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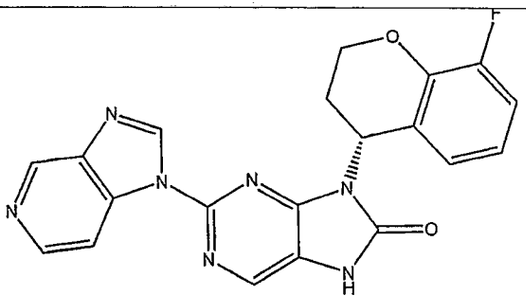
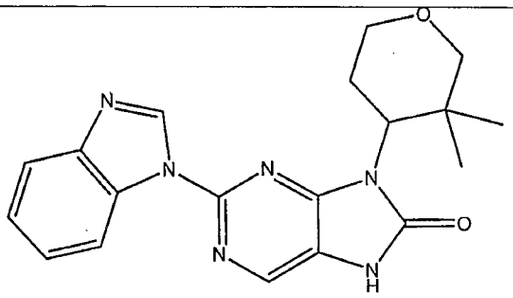
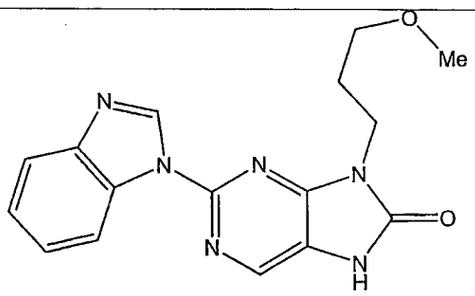
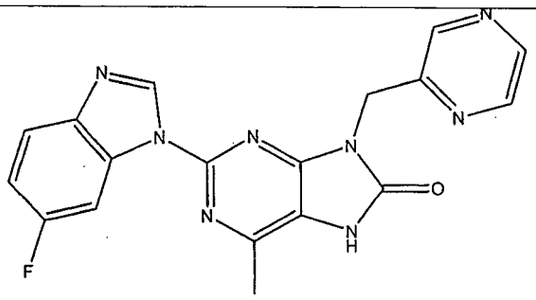
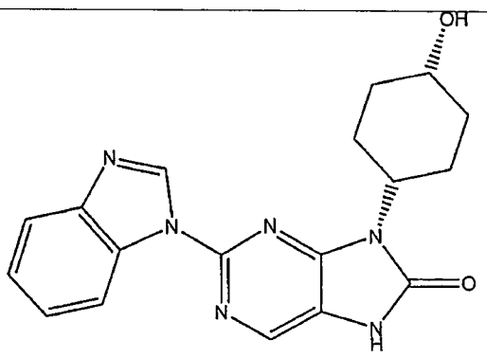
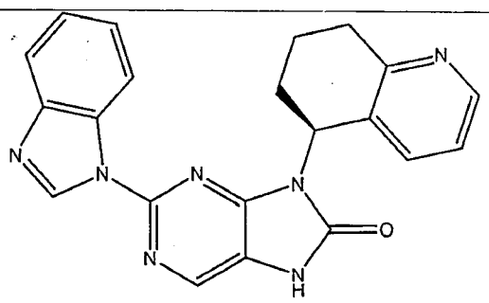
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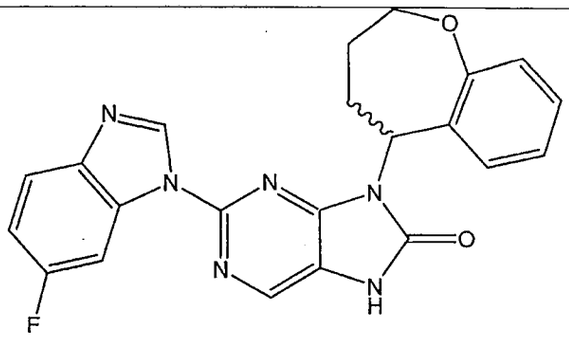
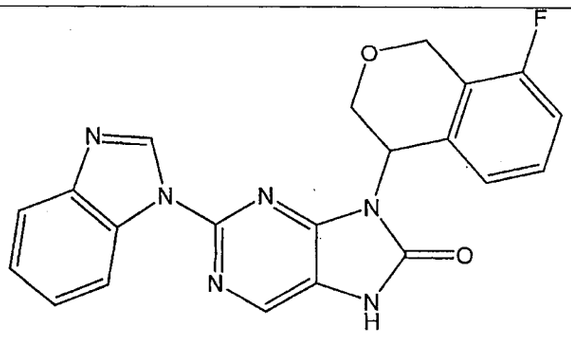
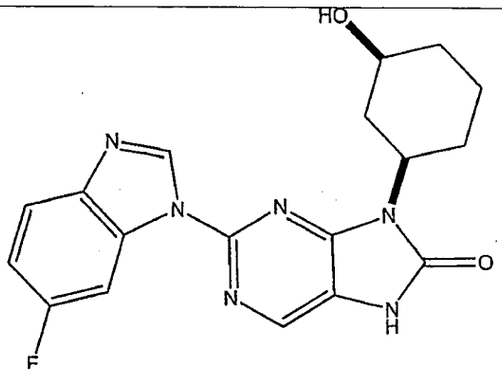
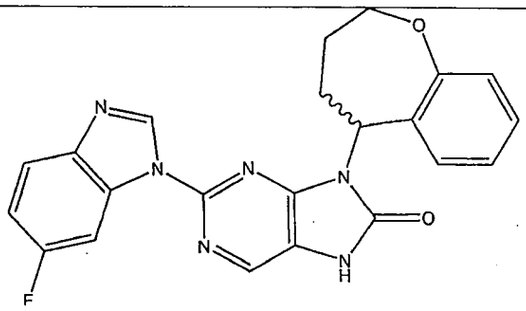
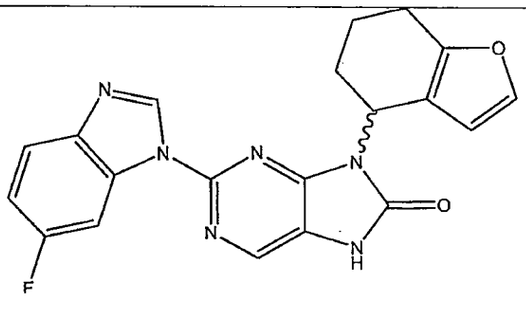
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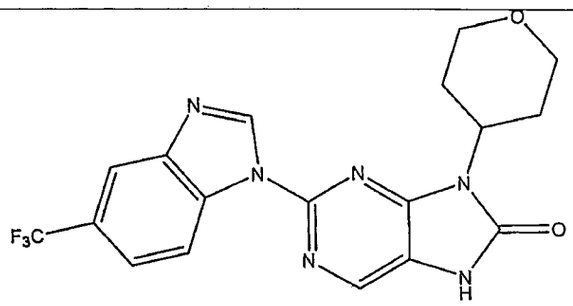
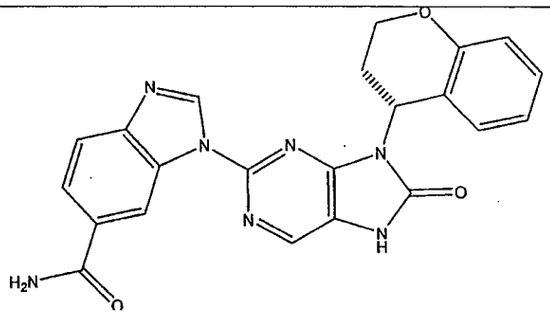
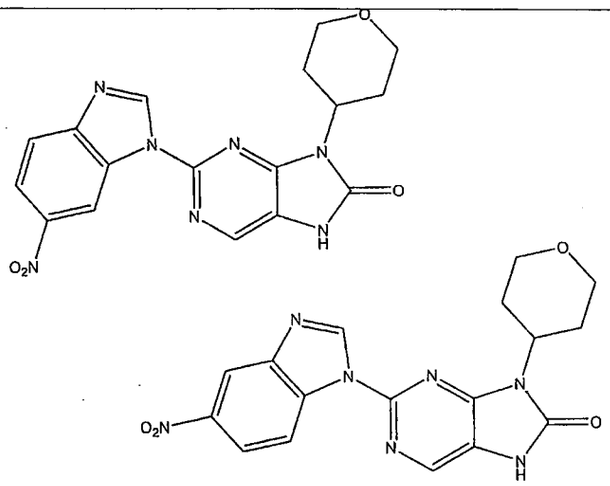
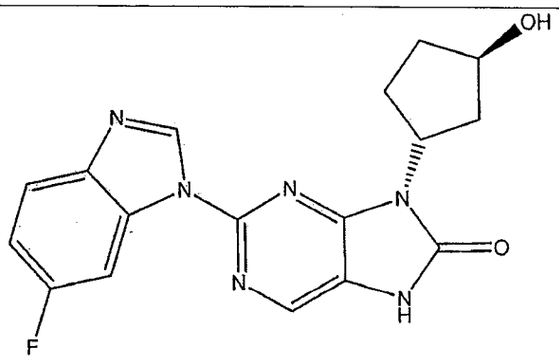
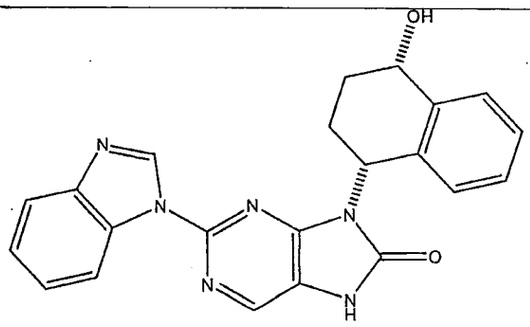
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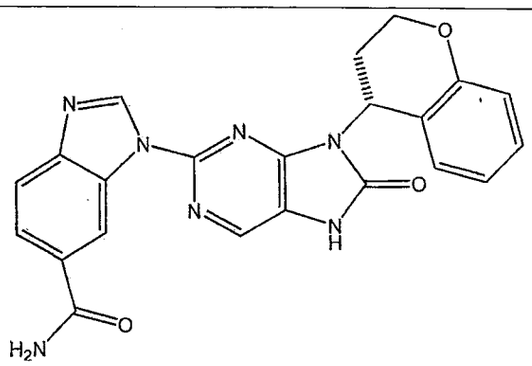
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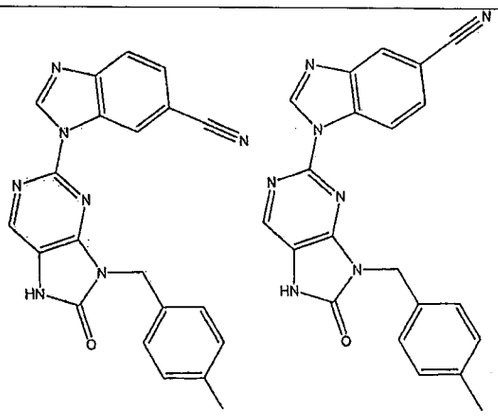
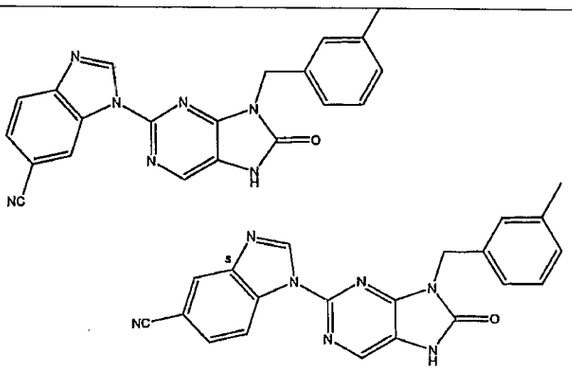
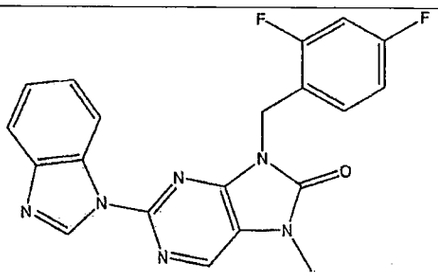
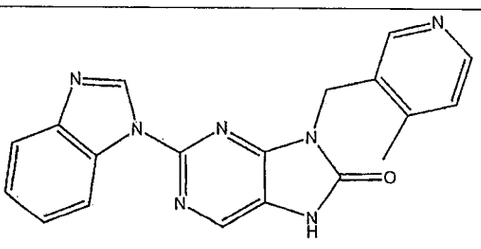
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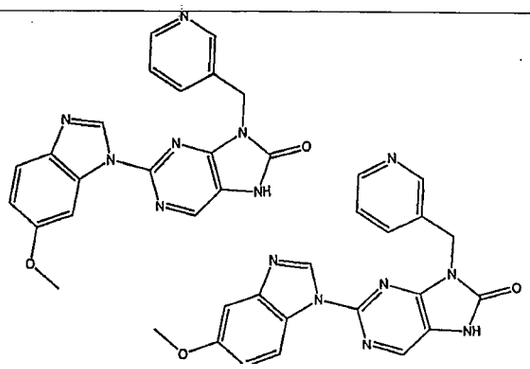
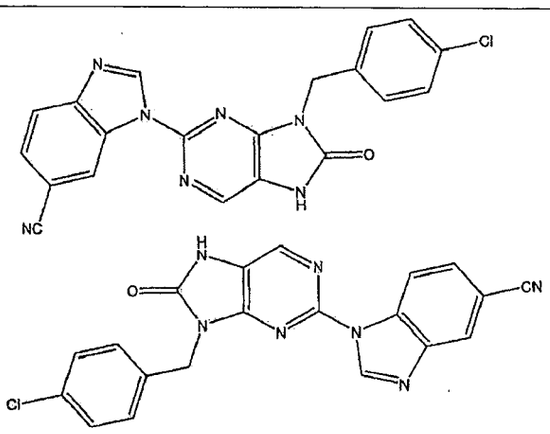
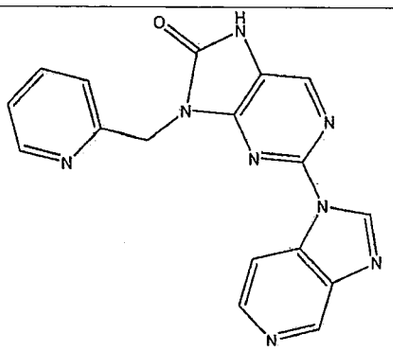
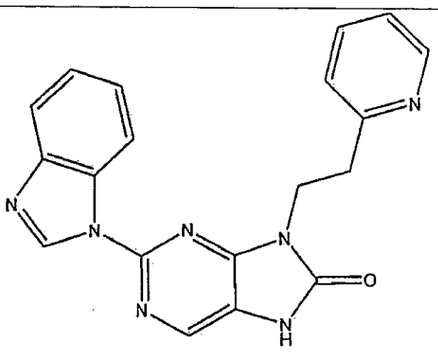
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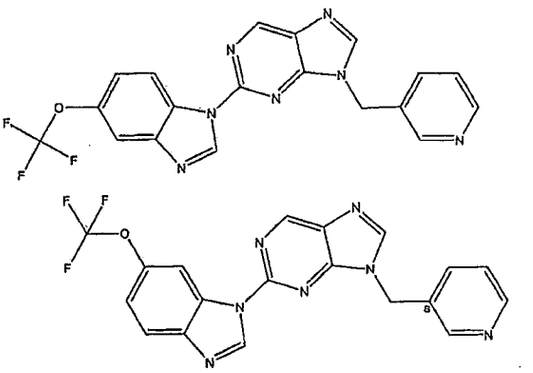
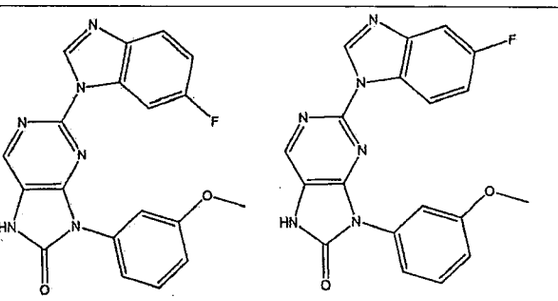
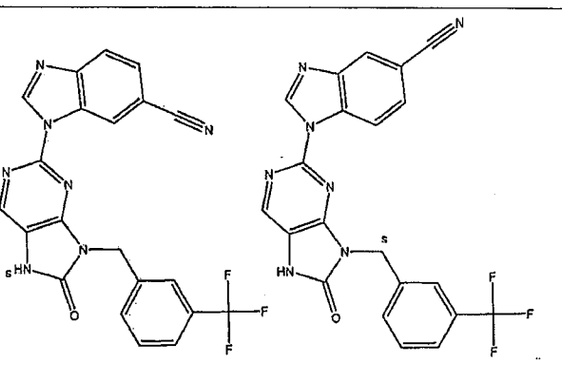
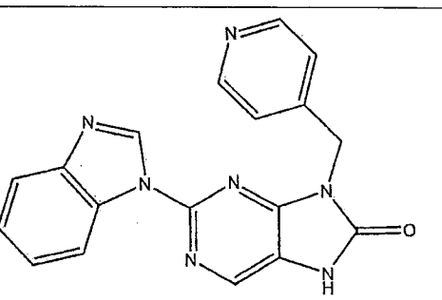
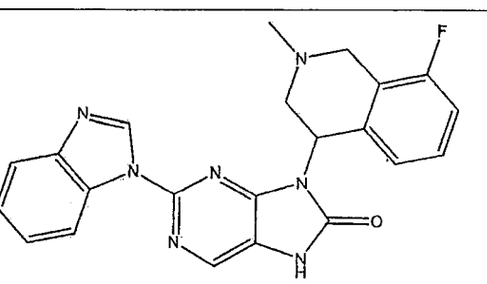
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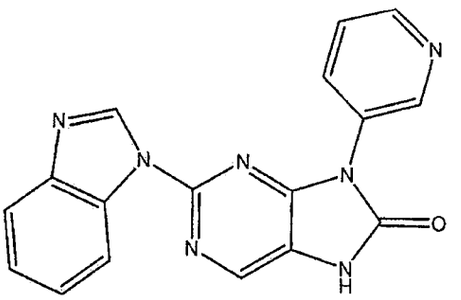
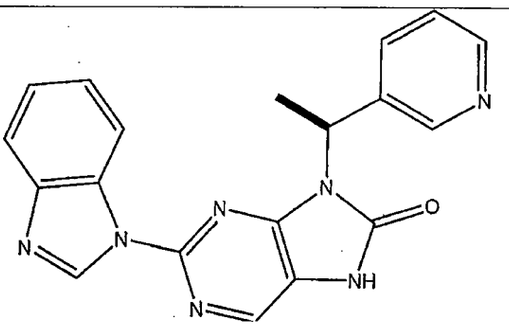
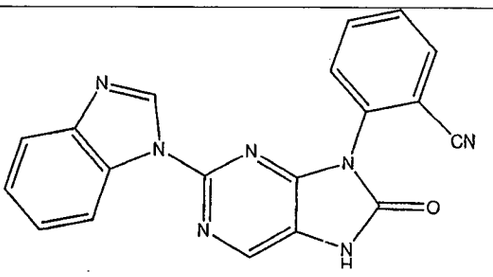
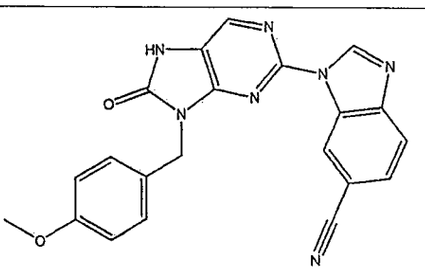
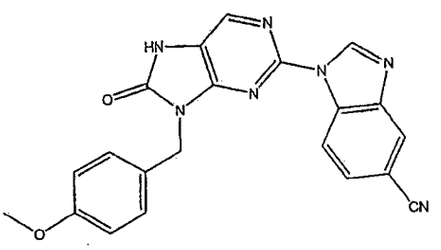
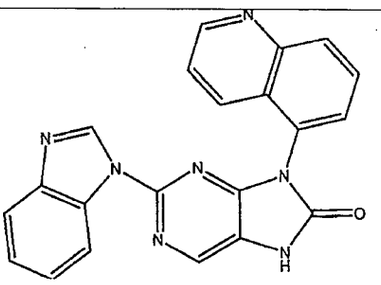
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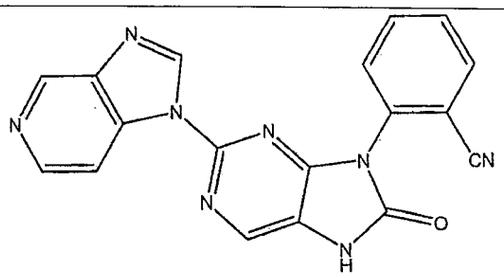
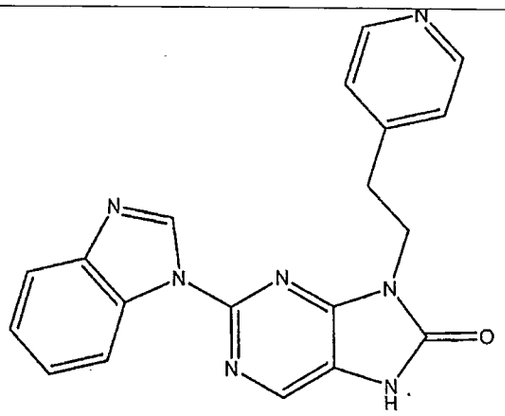
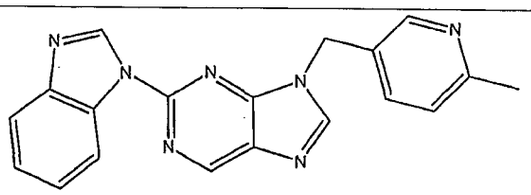
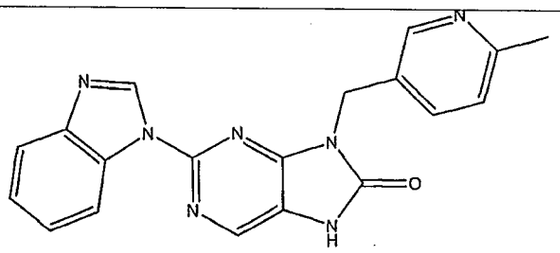
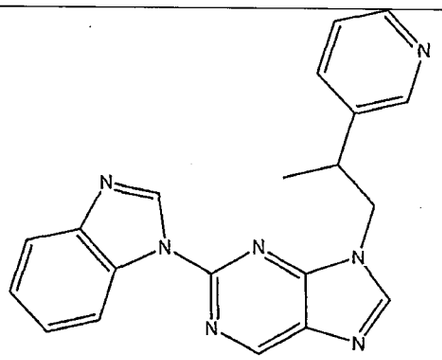
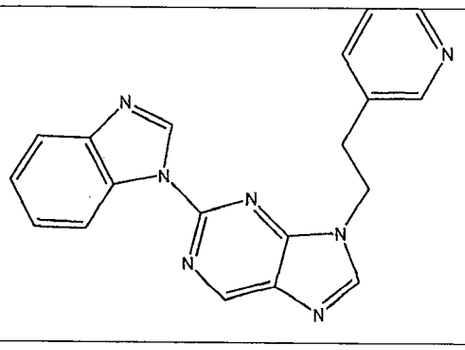
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Ejemplo de Síntesis	Referencia No.	TABLA 3
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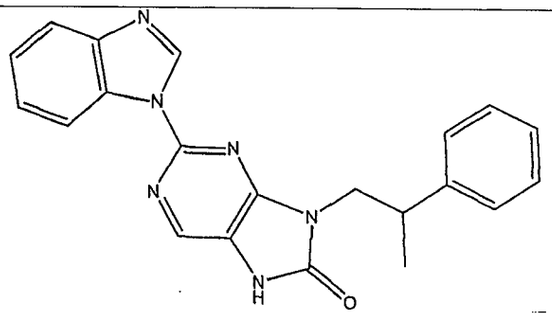
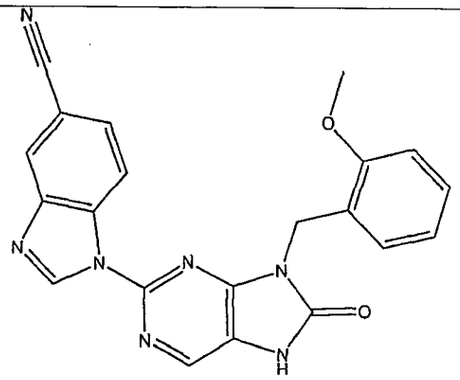
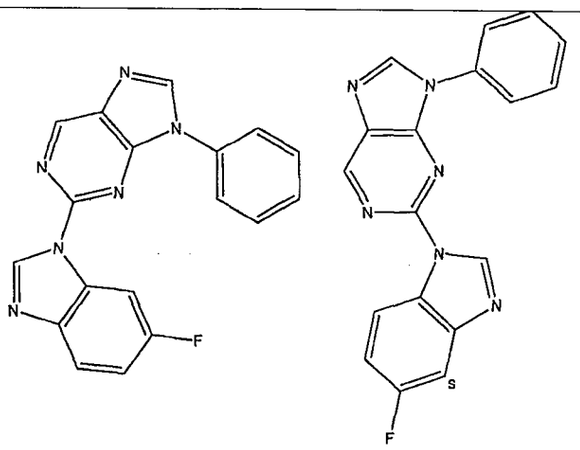
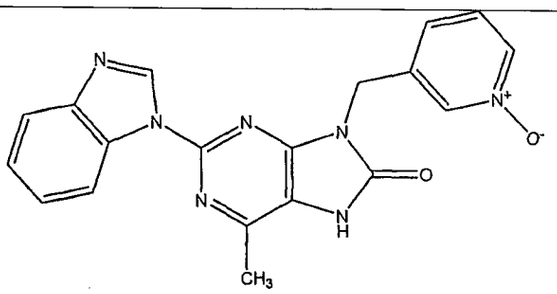
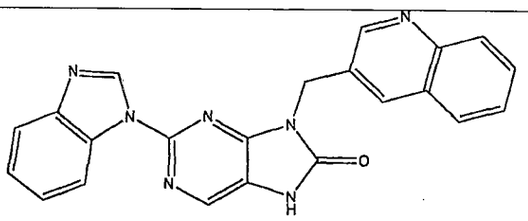
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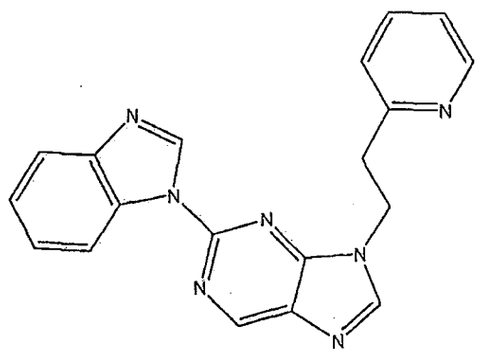
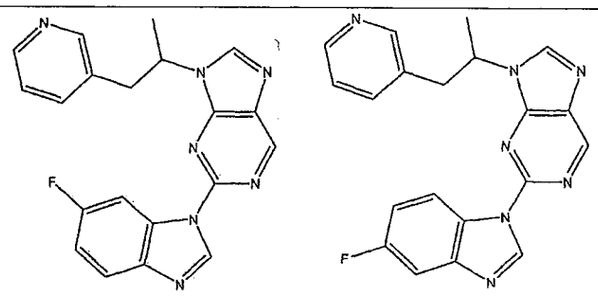
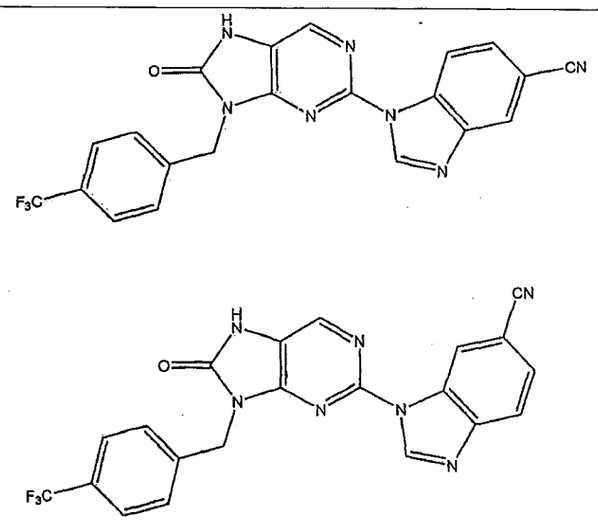
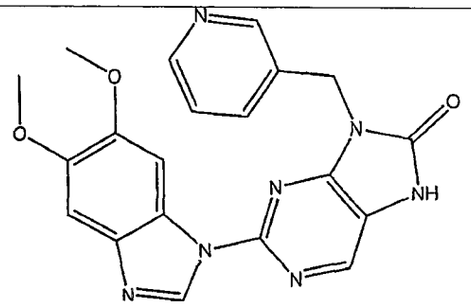
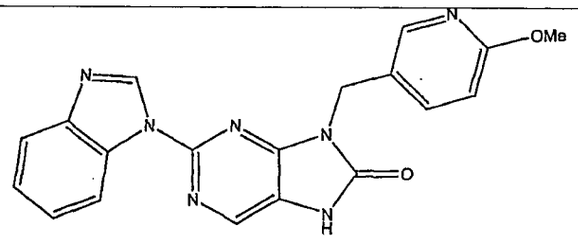
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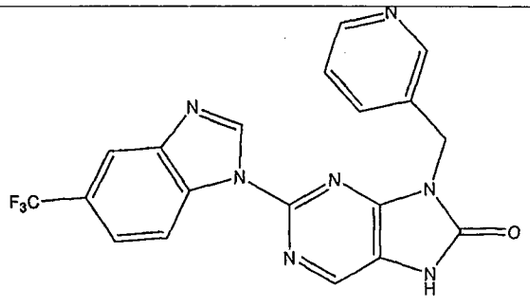
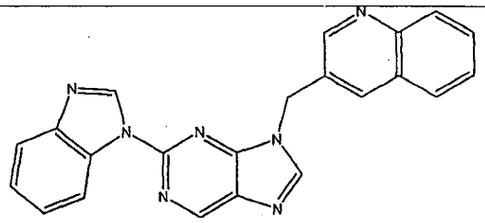
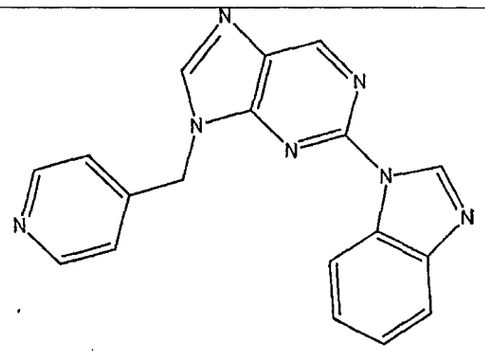
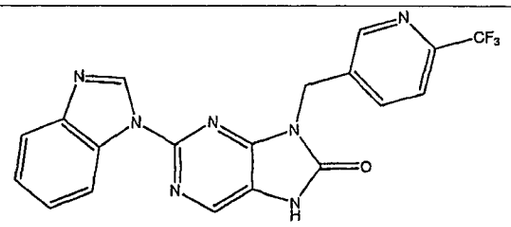
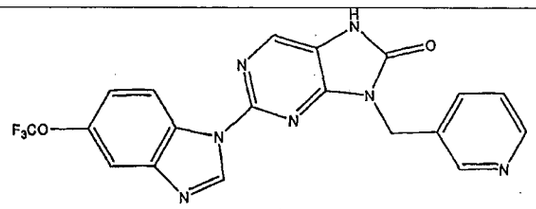
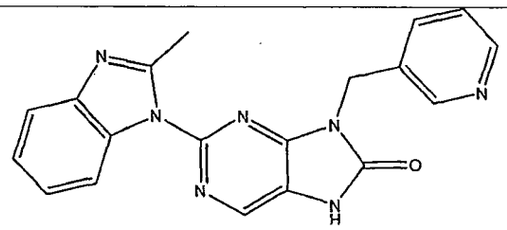
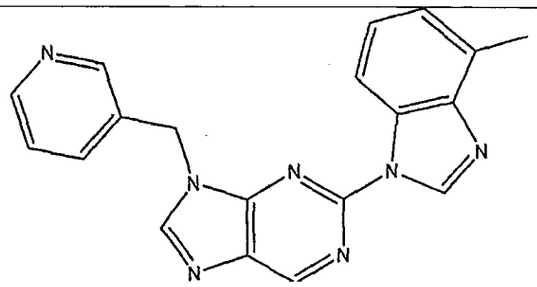
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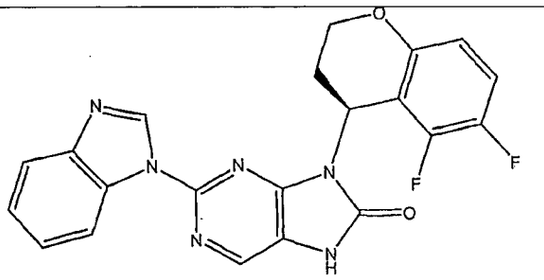
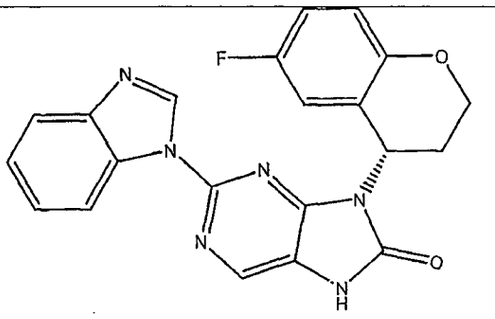
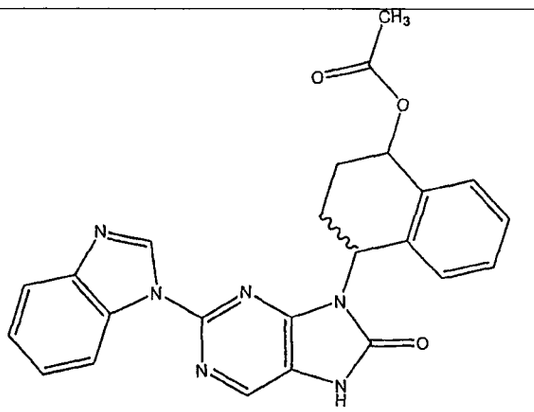
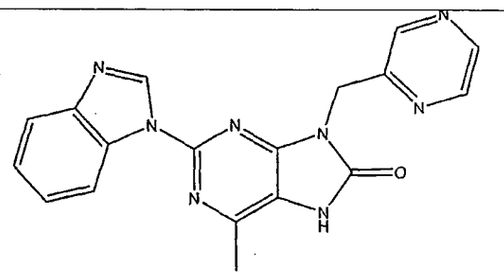
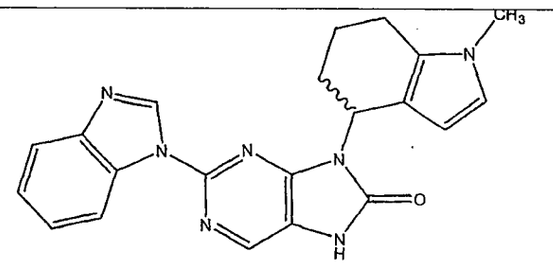
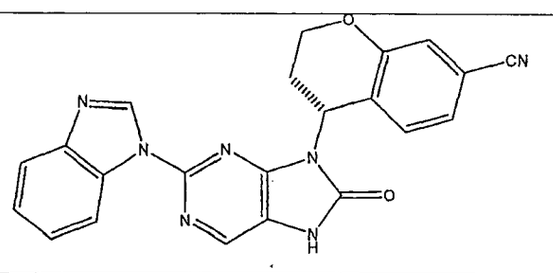
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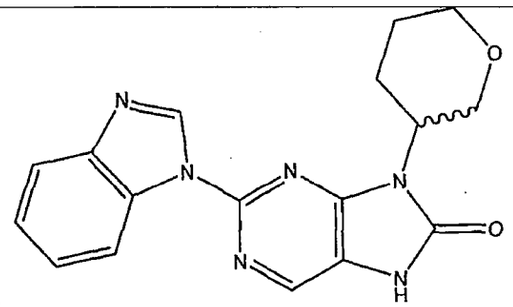
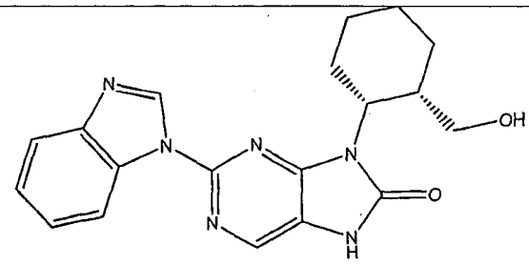
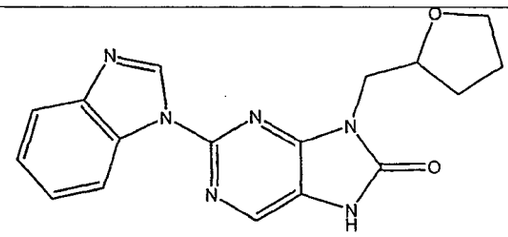
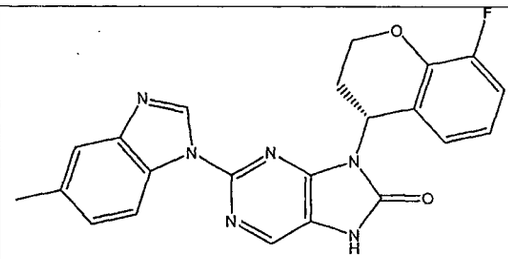
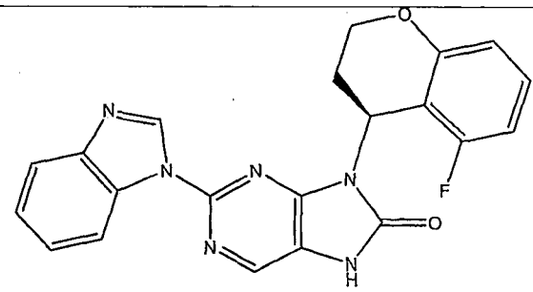
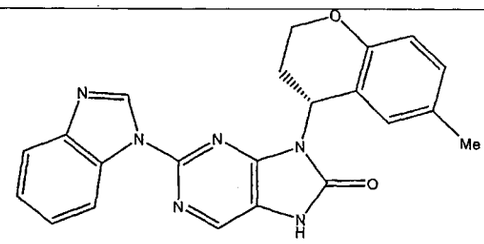
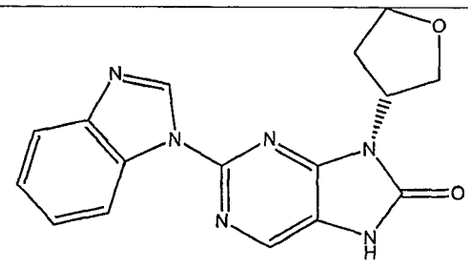
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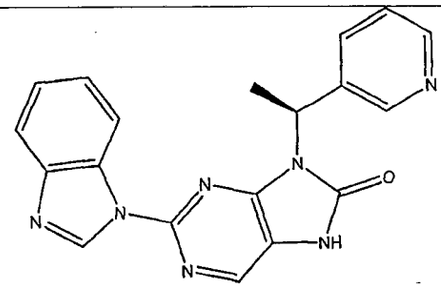
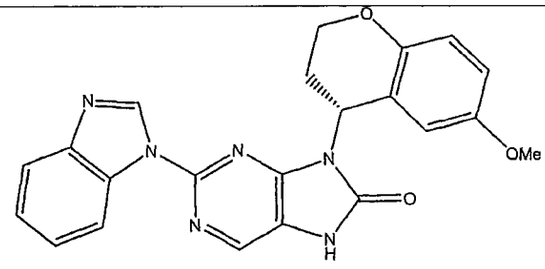
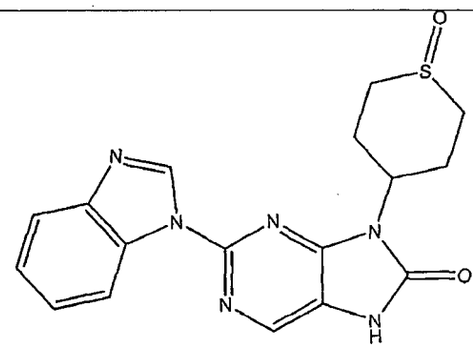
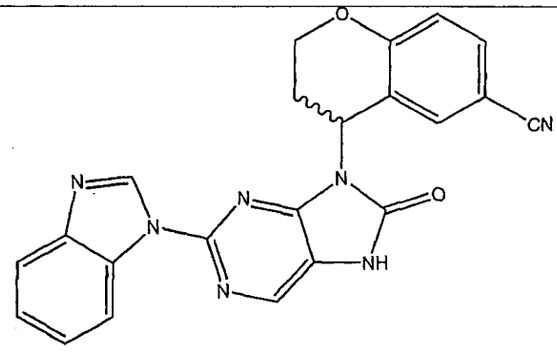
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Producción de IFN-γ inducido por IL-2 en el ratón

[395] La administración de IL-2 lleva a un aumento en el IFN-γ sérico en el ratón debido a la secreción de NK de la citocina (Thornton S, Kuhn KA, Finkelman FD y Hirsch R. NK cells secrete high levels of IFN-γ in response to *in vivo* administration of IL-2. Eur J Immunol 2001 31:3355-3360). El experimento se llevó a cabo esencialmente de acuerdo con el protocolo en Thornton et al., y se administraron los compuestos de prueba con el fin de determinar el nivel de inhibición obtenida. En síntesis, ratones BALB/c hembra se privaron de comida 12-18 horas antes de un estudio

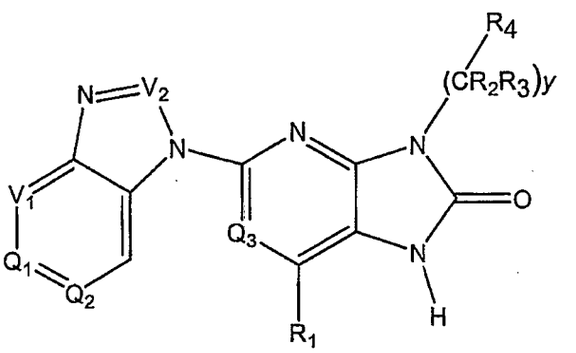
pero tuvieron acceso libre a agua todas las veces. Los compuestos de prueba se administraron por sonda gástrica una hora antes de la inyección intraperitoneal de IL-2 y anticuerpo de captura. A la terminación de los estudios, los ratones se sacrificaron por inhalación de dióxido de carbono, se recogieron muestras de sangre terminal mediante punción cardiaca y se generó suero. Se almacenó el suero congelado hasta que se analizó con respecto a IFN-γ, como se describe por el fabricante del kit (BD Pharmingen™, San Diego, CA).

[396] Usando el método anterior, los compuestos 114, 120, 135, 137, 138, 139, 142, 143, 151, y 162 de la Tabla 1 demostraron inhibir la producción de IFN-gamma inducida por en >40% a 30 mg/kg *in vivo* en el ratón. Un compuesto de referencia, CP690550, exhibió una inhibición del 96% a 30 mg/kg en este cribado.

[397] Aunque la invención precedente se ha descrito con algún detalle para efectos de ilustración, será fácilmente evidente a una persona experta en el arte que pueden introducirse cambios y modificaciones sin apartarse del ámbito de la invención descrita en esta solicitud.

REIVINDICACIONES

1. Un compuesto de fórmula I



I

en donde

Q_1 y Q_2 se seleccionan independientemente del grupo conformado por CX_1, CX_2, y nitrógeno;

Q_3 es N o CH;

X_1 y X_2 se seleccionan independientemente del grupo conformado por hidrógeno, $(C_1\text{-}C_6)$alquilo, ciano, halo, halo$(C_1\text{-}C_6)$alquilo, hidroxilo, $(C_1\text{-}C_6)$alcoxi, halo$(C_1\text{-}C_6)$alcoxi, nitro, carboxamido, y metilsulfonilo;

V_1 y V_2 se seleccionan independientemente de CH y N;

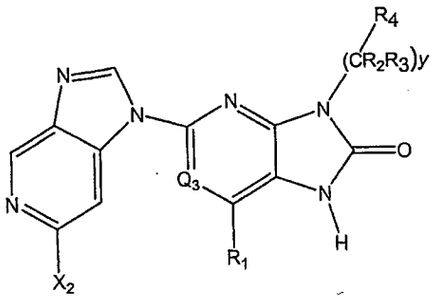
R_1 se selecciona del grupo conformado por hidrógeno y metilo;

y es cero o un entero seleccionado de 1, 2 y 3;

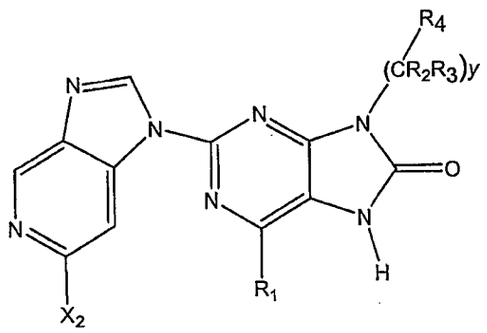
R_2 y R_3 se seleccionan independientemente para cada ocurrencia de (CR_2R_3) del grupo conformado por hidrógeno y $(C_1\text{-}C_6)$alquilo; y

R_4 se selecciona de un grupo conformado por alquilo, heterociclilo, arilo, alquilo sustituido, heterociclilo sustituido, y arilo sustituido.

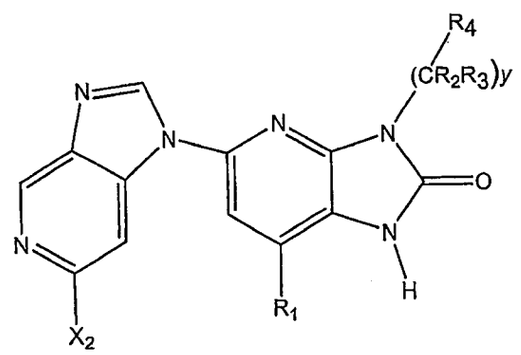
2. Un compuesto de acuerdo con la reivindicación 1 de fórmula:



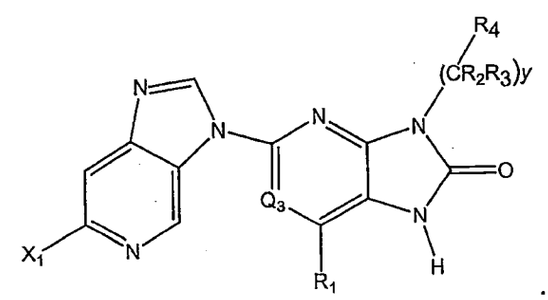
3. Un compuesto de acuerdo con la reivindicación 2 de fórmula:



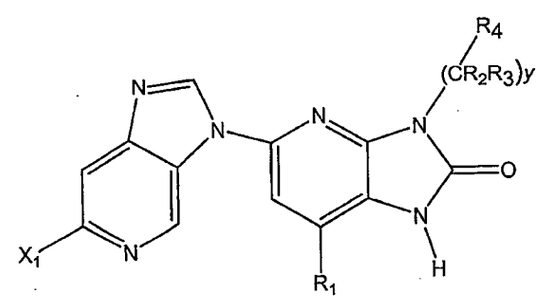
4. Un compuesto de acuerdo con la reivindicación 2 de fórmula:



5. Un compuesto de acuerdo con la reivindicación 1 de fórmula:

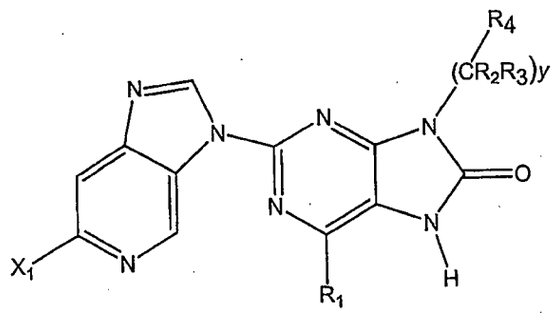


6. Un compuesto de acuerdo con la reivindicación 5 de fórmula:

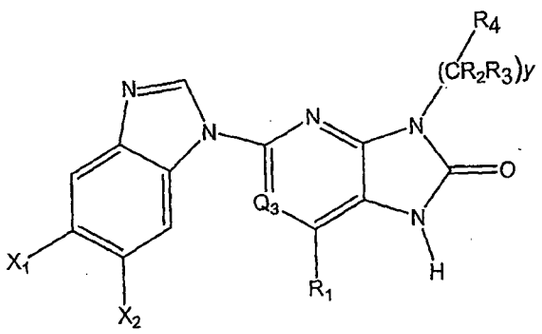


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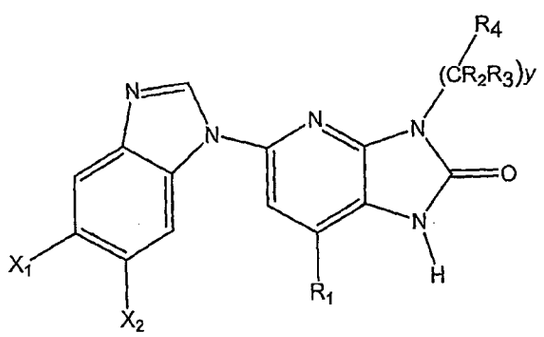
7. Un compuesto de acuerdo con la reivindicación 5 de fórmula:



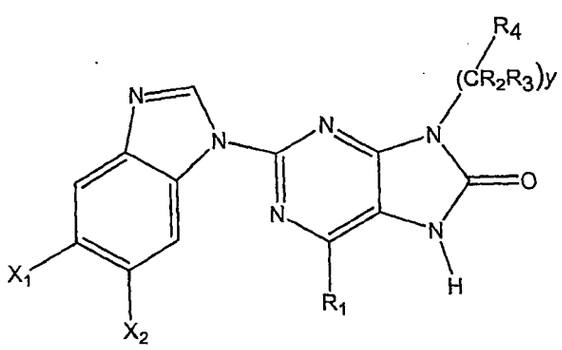
8. Un compuesto de acuerdo con la reivindicación 1 de fórmula:



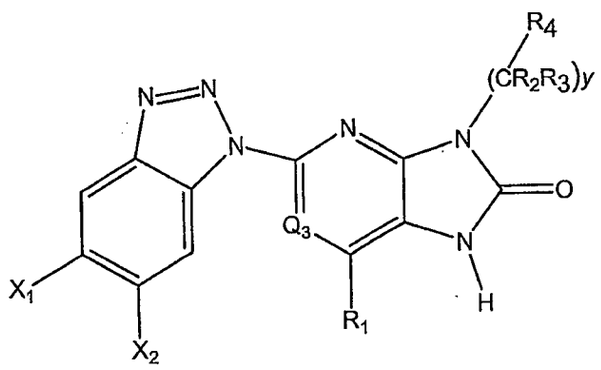
9. Un compuesto de acuerdo con la reivindicación 8 de fórmula:



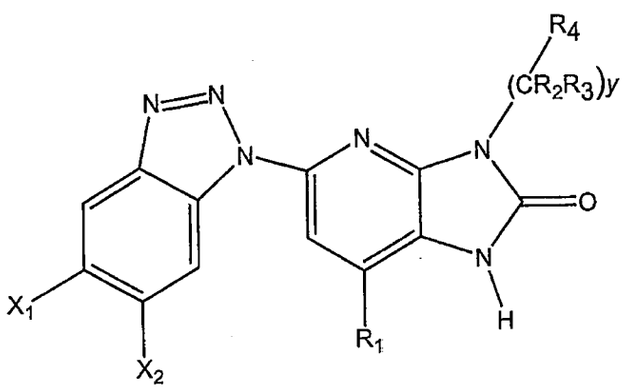
10. Un compuesto de acuerdo con la reivindicación 8 de fórmula:



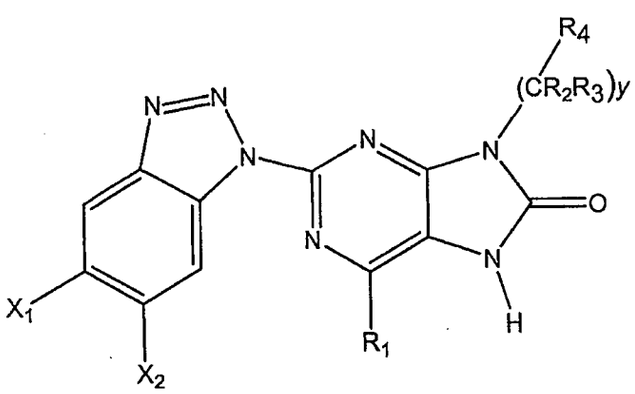
11. Un compuesto de acuerdo con la reivindicación 1 de fórmula:



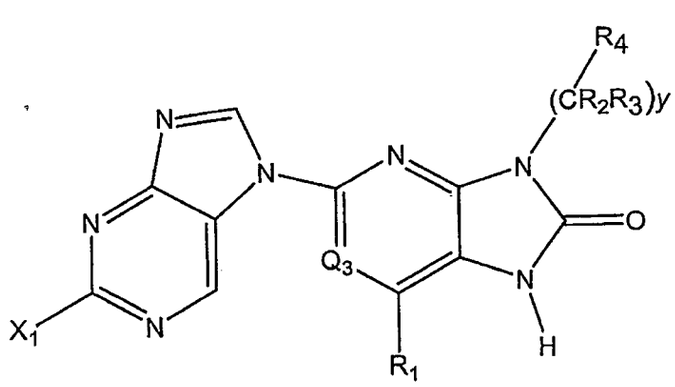
12. Un compuesto de acuerdo con la reivindicación 11 de fórmula:



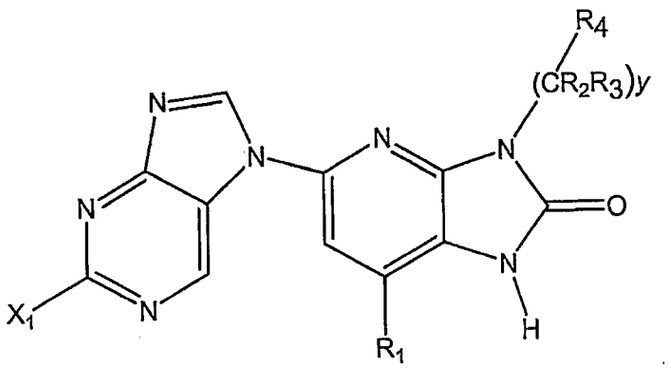
13. Un compuesto de acuerdo con la reivindicación 11 de fórmula:



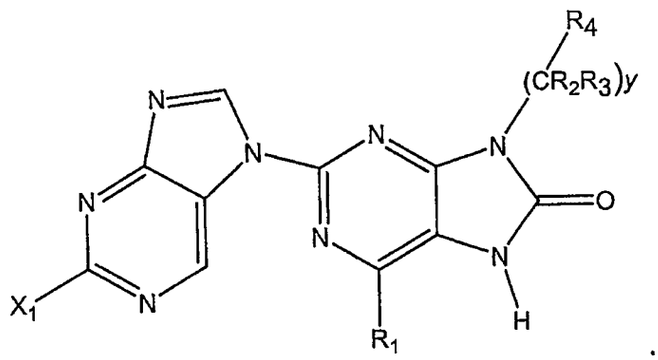
14. Un compuesto de acuerdo con la reivindicación 1 de fórmula:



15. Un compuesto de acuerdo con la reivindicación 14 de fórmula:



16. Un compuesto de acuerdo con la reivindicación 14 de fórmula:



17. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-16 en donde X_1 y X_2 se seleccionan independientemente de hidrógeno, ciano, cloro, fluoro, metilo, trifluorometilo y trifluorometoxi, carboxamido.

18. Un compuesto de acuerdo con cualquiera de las reivindicaciones 8-13 en donde X_1 es hidrógeno y X_2 se selecciona de hidrógeno, ciano, cloro, fluoro, metilo, carboxamido, y trifluorometilo.

19. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-16 en donde R_1 es H.

20. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-16 en donde, ***y*** es 1 ó 2 y R_2 y R_3 son hidrógeno o metilo.

21. Un compuesto de acuerdo con la reivindicación 20, en donde R_4 se selecciona de fenilo, quinolina, piridina, pirazina y sus contrapartes sustituidas.

22. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-16 en donde *y* es cero.

23. Un compuesto de acuerdo con la reivindicación 22, en donde R_4 se selecciona de a monociclo, biciclo, o monociclo sustituido o biciclo sustituido, que contiene por lo menos un átomo de oxígeno o un átomo de nitrógeno.

24. Un compuesto de acuerdo con la reivindicación 22, en donde R_4 se selecciona de ciclopentilo, ciclohexilo, fenilo, tetralina, piperidina, oxepano, benzoxepano, tetrahidropirano, tetrahidrofurano, tetrahidroindol, tetrahidroisoquinolina, quinolina, tetrahidroquinolina, cromano, piridina, dihidrociclopenta[b]piridina, dihidrobenzofurano, tetrahidrobenzofurano, tetrahidrobenzotiofeno, dihidrobenzotiofeno, dihidropirano[2,3-b]piridina, tetrahidroquinoxalina, tetrahidrothiopirano (tiano), tiocromano (dihidrobenzotiína), tiocroman-1,1-dióxido, tetrahidronaftaleno, oxa-biciclooctano, oxocano, tetratiohidropiran-1,1-dióxido, tetratiohidropiranóxido, y sus contrapartes sustituidas.

25. Un compuesto de acuerdo con la reivindicación 22, en donde R_4 es cicloalquilo sustituido con OH, alcoxi, hidroxialquilo, oxo, carboxamido, carboxi, o alcoxicarbonilo.

26. Un compuesto de acuerdo con la reivindicación 22 en donde R_4 se selecciona de ciclopentilo, ciclohexilo, fenilo, indano, tetralina, piperidina, oxepano, benzoxepano, dihidrociclopentapiridina, tetrahidropirano, tetrahidrofurano, tetrahidroindol, isoquinolina, tetrahidroisoquinolina, quinolina, tetrahidroquinolina, cromano, isocromano, piridina, dihidrociclopental[b]piridina, pirimidina, dihidropirano, dihidrobenzofurano, tetrahidrobenzofurano, tetrahidrobenzotiofeno, dihidrobenzotiofeno, furano, dihidropirano[2,3-b]piridina,

tetrahidroquinoxalina, tetrahidrothiopirano (tiano), tiocromano (dihidrobenzotiína), thiocroman-1,1-dióxido, tetrahidronaftaleno, oxa-biciclooctano, oxocano, tetrahidrothiopiran-1,1-dióxido, tetrahidrotiopiranóxido, y sus contrapartes sustituidas.

27. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-16 en donde,

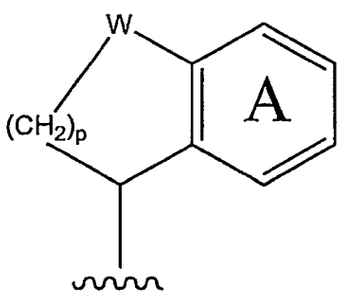
(a) *y* es cero y R_4 se selecciona de ciclohexilo, tetralina, indano, oxepano, benzoxepano, dihidrociclopentapiridina, tetrahidropirano, tetrahidroquinolina, cromano, dihidrobenzofurano, tetrahidrobenzofurano, dihidropirano[2,3-b]piridina y tetrahidroquinoxalina, sustituido cada uno opcionalmente con hidroxi, oxo, o halógeno; o

(b) *y* es 1 ó 2, R_2 y R_3 son hidrógeno o metilo y R_4 se selecciona de fenilo, piridina y pirazina, sustituido cada uno opcionalmente con halógeno.

28. Un compuesto de acuerdo con la reivindicación 27 en donde *y* es 0 y R_4 se selecciona de croman-4-ilo; 3,4-dihidronaftalen-1(2*H*)-on-4-ilo; 2,3-dihidroinden-1-on-4-ilo y sus contrapartes fluoro sustituidas.

29. Un compuesto de acuerdo con la reivindicación 28 en donde R_4 es croman-4-ilo y el carbono en la posición 4 del cromano es de la configuración (R).

30. Un compuesto de acuerdo con la reivindicación 27 en donde *y* es 0 y R_4 es



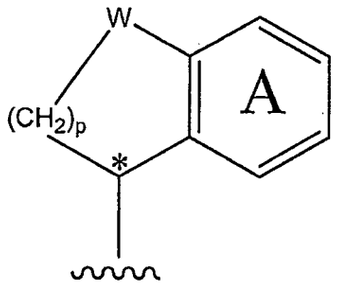
en donde

W es CH_2, C=O, O, y CHOH;

p es 1, 2 ó 3;

A es un anillo heteroaromático de seis miembros, que contiene 1 ó 2 nitrógenos, un anillo benceno sustituido opcionalmente con uno o dos flúoros, o un anillo heterocíclico de cinco miembros; y la línea ondulada es el punto de enlace a la purinona.

31. Un compuesto de acuerdo con la reivindicación 30 en donde el carbono marcado con un asterisco



es de la configuración (R).

32. Un compuesto de acuerdo con la reivindicación 1, en donde Y es 0 y R_4 es un carbociclo monocíclico o carbociclo bicíclico puenteado sustituido opcionalmente con uno o más OH, alcoxi, hidroxialquilo, oxo, carboxamido, carboxi, y alcoxicarbonilo.

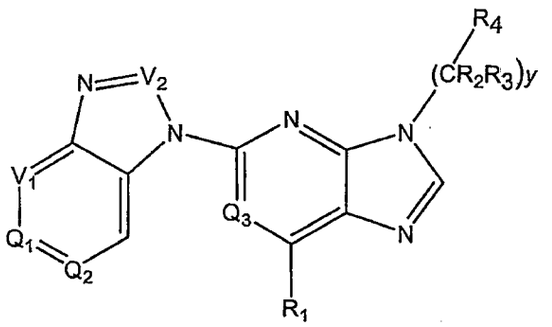
33. Un compuesto de acuerdo con la reivindicación 1, en donde Y es 0 y R_4 es un heterociclo que contiene por lo menos un átomo de nitrógeno y sustituido opcionalmente con OH, alcoxi, hidroxialquilo, oxo, acilo, carboxamido, carboxi, y alcoxicarbonilo.

34. Un compuesto de acuerdo con la reivindicación 33, en donde R_4 es un heterociclo monocíclico.

35. Un compuesto de acuerdo con la reivindicación 27 en donde *y* es 1 y R_4 se selecciona de difluorofenilo, fluorofenilo, clorofenilo, clorofluorofenilo, piridin-3-ilo y pirazin- 3-ilo.

36. Un compuesto de acuerdo con la reivindicación 27 en donde *y* es cero y R_4 se selecciona de tetrahidropiran-4-ilo, 4-hidroxiciclohexilo, 4-alcoxi inferior ciclohexilo, 4-oxociclohexilo y oxepan-4-ilo.

37. Un compuesto de fórmula II



II

en donde

Q_1 y Q_2 se seleccionan independientemente del grupo conformado por CX_1, CX_2, y nitrógeno;

Q_3 es N o CH;

X_1 y X_2 se seleccionan independientemente del grupo conformado por hidrógeno, $(C_1\text{-}C_6)$alquilo, ciano, halo, halo$(C_1\text{-}C_6)$alquilo, hidroxilo, $(C_1\text{-}C_6)$alcoxi, halo$(C_1\text{-}C_6)$alcoxi, nitro, carboxamido, y metilsulfonilo;

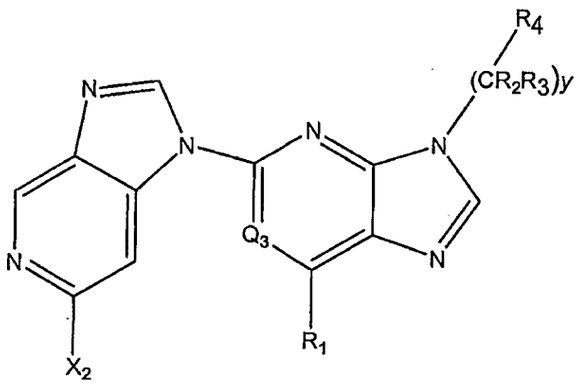
V_1 y V_2 se seleccionan independientemente de CH y N;

R_1 se selecciona del grupo conformado por hidrógeno y metilo; *y* es cero o un entero seleccionado de 1, 2 y 3;

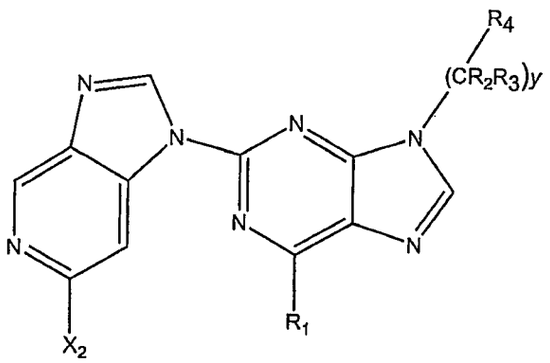
R_2 y R_3 se seleccionan independientemente para cada ocurrencia de (CR_2R_3) del grupo conformado por hidrógeno y $(C_1\text{-}C_6)$alquilo; y

R_4 se selecciona de un grupo conformado por alquilo, heterociclilo, arilo, alquilo sustituido, heterociclilo sustituido, y arilo sustituido.

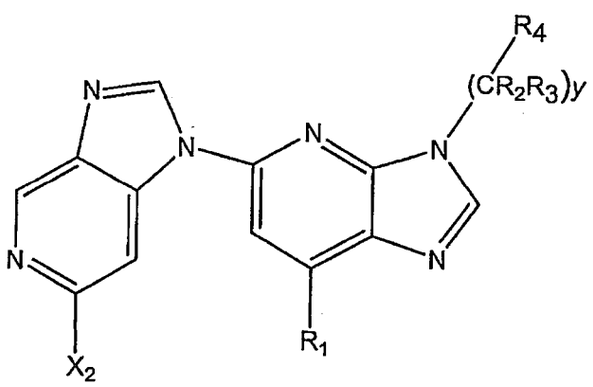
38. Un compuesto de acuerdo con la reivindicación 37 de fórmula:



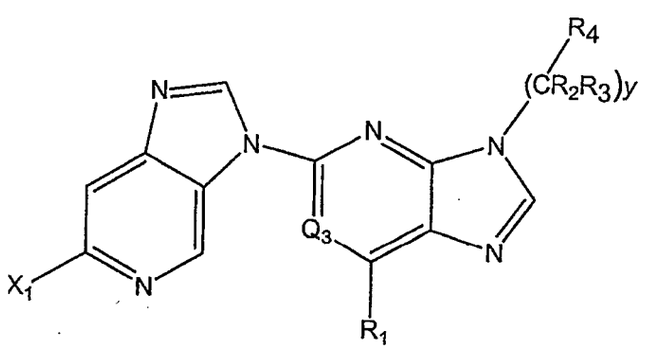
39. Un compuesto de acuerdo con la reivindicación 38 de fórmula:



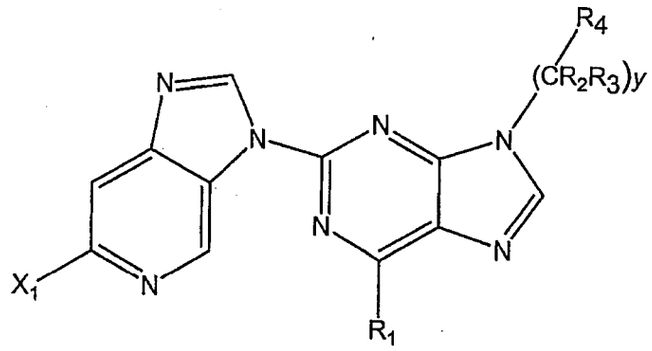
40. Un compuesto de acuerdo con la reivindicación 38 de fórmula:



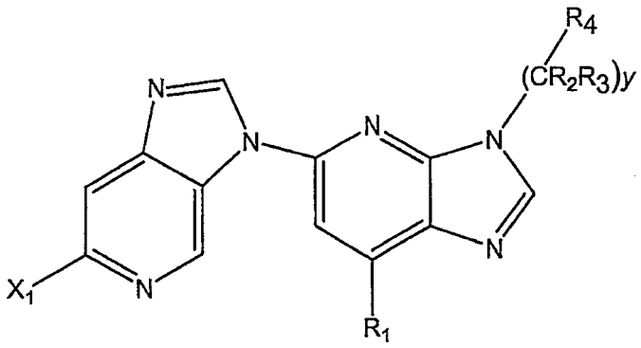
41. Un compuesto de acuerdo con la reivindicación 37 de fórmula:



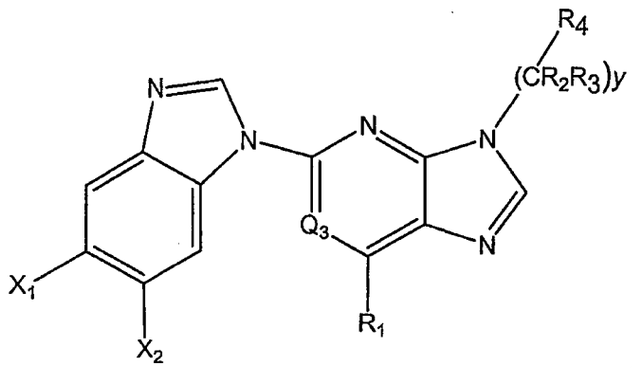
42. Un compuesto de acuerdo con la reivindicación 41 de fórmula:



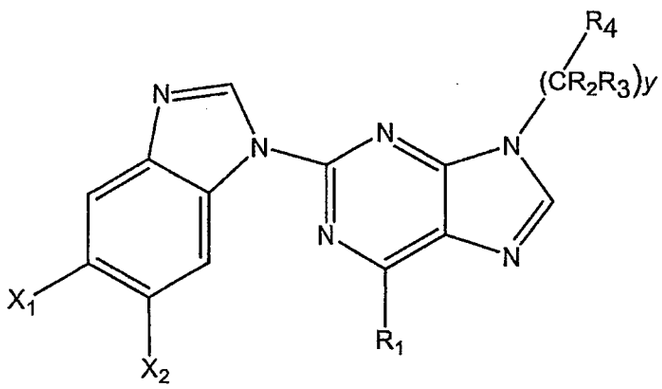
43. Un compuesto de acuerdo con la reivindicación 41 de fórmula:



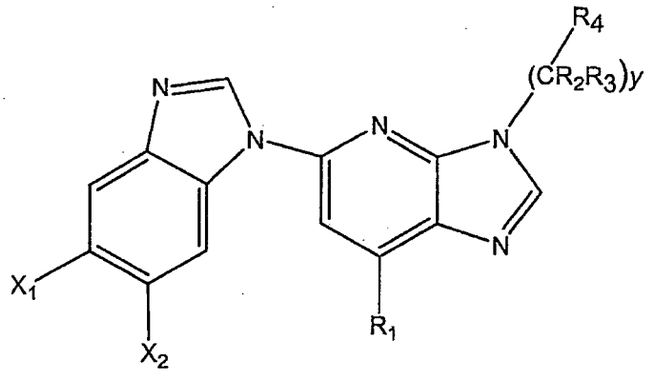
44. Un compuesto de acuerdo con la reivindicación 37 de fórmula:



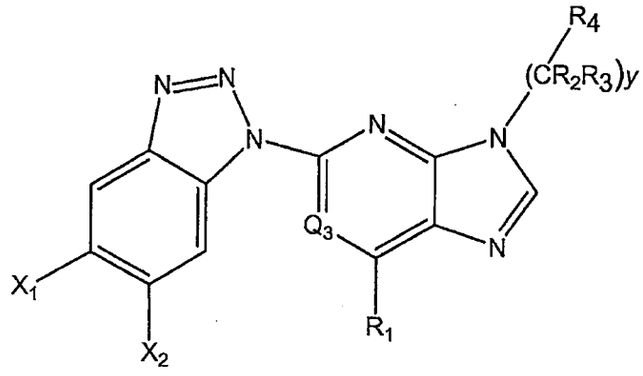
45. Un compuesto de acuerdo con la reivindicación 44 de fórmula:



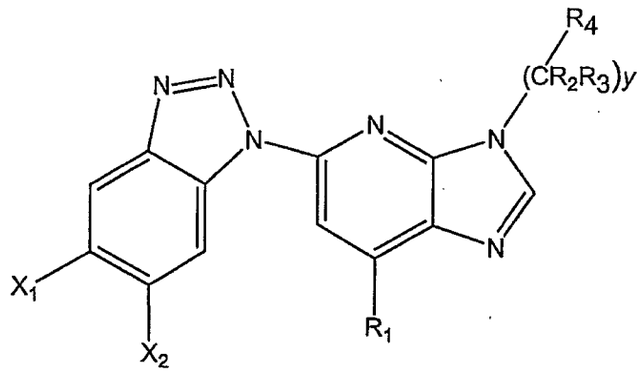
46. Un compuesto de acuerdo con la reivindicación 44 de fórmula:



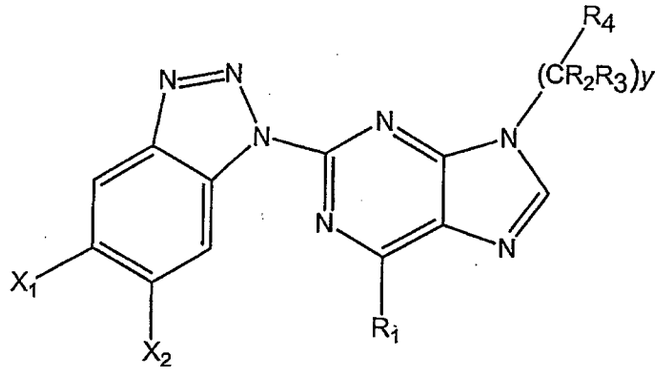
47. Un compuesto de acuerdo con la reivindicación 37 de fórmula:



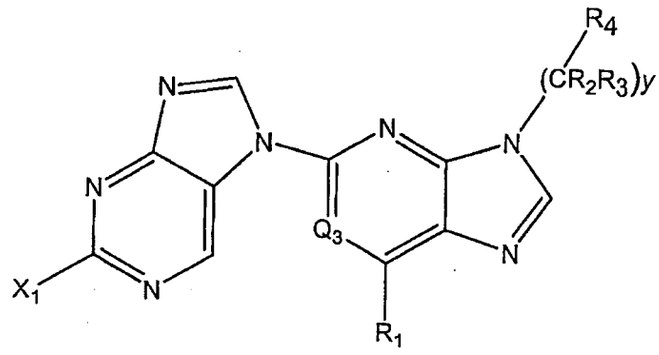
48. Un compuesto de acuerdo con la reivindicación 47 de fórmula:



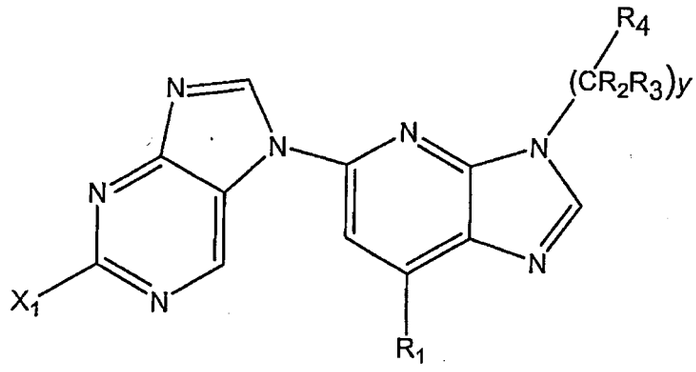
49. Un compuesto de acuerdo con la reivindicación 47 de fórmula:



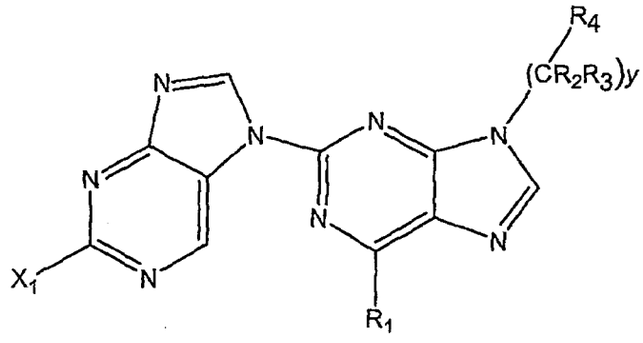
50. Un compuesto de acuerdo con la reivindicación 37 de fórmula:



51. Un compuesto de acuerdo con la reivindicación 50 de fórmula:



52. Un compuesto de acuerdo con la reivindicación 50 de fórmula:



53. Un compuesto de acuerdo con cualquiera de las reivindicaciones 37-52 en donde X_1 y X_2 se seleccionan independientemente de hidrógeno, ciano, fluoro, metilo, trifluorometilo, carboxamido, y trifluorometoxi.

54. Un compuesto de acuerdo con cualquiera de las reivindicaciones 37-52 en donde R_1 es H.

55. Un compuesto de acuerdo con cualquiera de las reivindicaciones 37-52 en donde *y* es 1 ó 2 y R_2 y R_3 son hidrógeno o metilo.

56. Un compuesto de acuerdo con la reivindicación 55 en donde R_4 se selecciona de fenilo, piridina, pirazina, quinolina y sus contrapartes sustituidas.

57. Un compuesto de acuerdo con cualquiera de las reivindicaciones 37-52 en donde *y* es cero.

58. Un compuesto de acuerdo con la reivindicación 57 en donde R_4 se selecciona de un monociclo, biciclo, o monociclo sustituido o biciclo sustituido, que contiene por lo menos un átomo de oxígeno y un átomo de nitrógeno.

59. Un compuesto de acuerdo con la reivindicación 57 en donde R_4 se selecciona de cromano, tetrahidropirano, quinolina, tetrahidroquinolina, y fenilo.

60. Un compuesto de acuerdo con la reivindicación 57 en donde R_4 se selecciona de fenilo, tetralina, indano, isoquinolina, tetrahidroquinolina, tetrahidropirano y sus contrapartes sustituidas.

61. Un compuesto de acuerdo con la reivindicación 55 en donde *y* es 1 y R_4 se selecciona de difluorofenilo, fluorofenilo, clorofenilo, clorofluorofenilo, piridin-3-ilo y pirazin-3-ilo.

62. Un compuesto de acuerdo con la reivindicación 55 en donde *y* es cero y R_4 se selecciona de croman-4-ilo; 3,4-dihidronaftalen-1(2*H*)-on-4-ilo; 2,3-dihidroinden-1-on-4-ilo y sus contrapartes fluoro sustituidas.

63. Un compuesto de acuerdo con la reivindicación 55 en donde *y* es cero y R_4 es isoquinolin-8-ilo o 1,2,3,4-tetrahidroquinolin-5-ilo.

64. Una composición farmacéutica que comprende una sustancia portadora farmacéuticamente aceptable y una cantidad terapéuticamente efectiva de por lo menos un compuesto de acuerdo con cualquiera de las reivindicaciones 1-16 ó 37-52.

65. Un método de tratar un trastorno que es dependiente de la inhibición de la cinasa 3 Janus, que comprende administrar a un sujeto necesitado de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto de acuerdo con la reivindicación 1.

66. Un método de tratar un trastorno que es dependiente de la inhibición de la cinasa 3 Janus, que comprende administrar a un sujeto necesitado de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto de acuerdo con la reivindicación 37.

67. método de acuerdo con cualquiera de las dos reivindicaciones 65 ó 66 en donde dicho trastorno se selecciona de una enfermedad autoinmunitaria, una enfermedad inflamatoria, una enfermedad mediada por mastocitos, cáncer, neoplasia maligna hematológica, rechazo de transplante de órganos, y enfermedad cardiovascular.

68. El método de acuerdo con la reivindicación 67 en donde dicho trastorno es rechazo de trasplante de órganos.

69. El método de acuerdo con la reivindicación 67 en donde dicho trasplante de órganos es trasplante de riñón.

70. El método de acuerdo con la reivindicación 65 ó 66 en donde dicho trastorno es una neoplasia maligna no hematológica.

71. El método de acuerdo con la reivindicación 70 en donde dicho trastorno es cáncer de colon, cáncer de páncreas o linfoma.

72. El método de acuerdo con la reivindicación 67 en donde en donde dicho trastorno es psoriasis o artritis reumatoide.

73. El método de acuerdo con la reivindicación 67 en donde en donde dicho trastorno es queratoconjuntivitis seca.

74. El método de acuerdo con la reivindicación 67 en donde en donde dicho trastorno es enfermedad cardiovascular.

75. El método de acuerdo con la reivindicación 67 en donde dicha neoplasia maligna hematológica es leucemia mielógena crónica o linfoma anaplásico de células grandes.

76. El método de acuerdo con la reivindicación 65 ó 66 en donde en donde dicho trastorno es asma.

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HESLIN ROTHENBERG FARLEY & MESITI P.C.

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Daniel J. Feigelson

July 27, 2007

Facsimile Transmission
011-41-22-733-5428

The International Bureau of WIPO
34, chemin des Columbettes
1211 Geneva 20
Switzerland

Re: PCT Application Number PCT/US2006/12824
Title: Purine and Imidazopyridine Derivatives for Immunosuppression
Application Date: April 5, 2006
Agent's File Number: 1073.081BWO

Dear Sirs:

In accordance with Rule *92bis*.1 of PCT Regulations, the applicant respectfully requests that the International Bureau record a change in name of the applicant for the above-referenced PCT application.

The applicant, Pharmacopeia Drug Discovery, Inc. has changed its name to Pharmacopeia, Inc., as filed with the State of Delaware, Secretary of State, Division of Corporations on May 3, 2007. A copy of the recorded document is attached for your reference.

The 30-month date from the priority date of April 5, 2005 expires on October 5, 2007, so this request is timely filed.

Sincerely,

HESLIN ROTHENBERG FARLEY & MESITI P.C.

Philip E. Hansen

PEH/so
Enclosure – Certificate of Amendment (3 pages)

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "PHARMACOPEIA DRUG DISCOVERY, INC.", CHANGING ITS NAME FROM "PHARMACOPEIA DRUG DISCOVERY, INC." TO "PHARMACOPEIA, INC.", FILED IN THIS OFFICE ON THE THIRD DAY OF MAY, A.D. 2007, AT 9:58 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

3493624 8100

070513274



Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 5645069

DATE: 05-03-07

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State of Delaware
Secretary of State
Division of Corporations
Delivered 10:05 AM 05/03/2007
FILED 09:58 AM 05/03/2007
SRV 070513274 - 3493624 FILE

CERTIFICATE OF AMENDMENT
OF THE
AMENDED AND RESTATED CERTIFICATE OF INCORPORATION
OF
PHARMACOPEIA DRUG DISCOVERY, INC.

****

PHARMACOPEIA DRUG DISCOVERY, INC., a corporation organized and existing under the General Corporation Law of the State of Delaware (the "Corporation"), does hereby certify:

FIRST: That by written consent of the board of directors dated March 16, 2007, resolutions were duly adopted setting forth a proposed amendment to the Amended and Restated Certificate of Incorporation of the Corporation, declaring said amendment to be advisable and calling for consideration of said proposed amendment by the stockholders of the Corporation at the next annual meeting of stockholders. The resolution setting forth the amendment is as follows:

> RESOLVED, that it is hereby proposed that Article One of the Amended and Restated Certificate of Incorporation of the Corporation be amended and restated in its entirety to read as follows:
>
> "*ONE*. The name of this corporation is 'Pharmacopeia, Inc.'"

SECOND: That thereafter, pursuant to the resolutions of the board of directors, the proposed amendment was approved by the stockholders of the Corporation at a meeting held on May 3, 2007.

THIRD: That said amendment was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

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IN WITNESS WHEREOF, the Corporation has caused this Certificate to be signed by Stephen C. Costalas, its Executive Vice President, General Counsel and Secretary, this 3rd day of May, 2007.

PHARMACOPEIA DRUG DISCOVERY, INC.

By: _____
Stephen C. Costalas
Executive Vice President, General
Counsel and Secretary

From the INTERNATIONAL BUREAU

4444

PCT

FIRST NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH DO NOT APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To: PEH/SSP

HANSEN, Philip
Heslin Rothenberg Farley & Mesiti P.C.
5 Columbia Circle
Albany, New York 12203
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 09 November 2006 (09.11.2006)	
Applicant's or agent's file reference 1073.081BWO	**IMPORTANT NOTICE**
International application No. PCT/US2006/012824	International filing date *(day/month/year)* 05 April 2006 (05.04.2006)
Priority date *(day/month/year)* 05 April 2005 (05.04.2005)	
Applicant PHARMACOPEIA DRUG DISCOVERY, INC. et al	

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
12 October 2006 (12.10.2006)

   CH

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

   LU, SE, TZ, UG, ZM

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

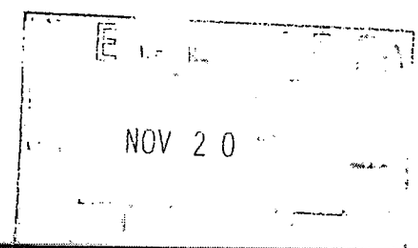
4. **TIME LIMITS for entry into the national phase**

   For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of **19 months** from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **20 MONTHS** from the priority date.

   In practice, **time limits other than the 20-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For **regular updates on the applicable time limits** (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   It is the applicant's **sole responsibility** to monitor all these time limits.

18/19/20/22 & 30 months
Untimely Lodged



The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Pct/ib/308

Authorized officer

Simin Baharlou

e-mail: pt09@wipo.int

PCT REQUEST

Original (for SUBMISSION)

4453

0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.51.005.180 MT/FOP 20060401/0.20.4rc.2.7
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**	1073.081BWO
I	**Title of Invention**	PURINE AND IMIDAZOPYRIDINE DERIVATIVES FOR IMMUNOSUPRRESION
II	**Applicant**	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	PHARMACOPEIA DRUG DISCOVERY, INC.
II-5	Address	3000 Eastpark Blvd. Cranbury, New Jersey 08512 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	(609) 452-3636
II-9	Facsimile No.	(609) 452-3672
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)	OHLMEYER, Michael
III-1-5	Address	6 Beechtree Lane Plainsboro, New Jersey 08536 United States of America
III-1-6	State of nationality	GB
III-1-7	State of residence	US

III-2	Applicant and/or Inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BOHNSTEDT, Adolph
III-2-5	Address	5 Red Fox Street Burlington, New Jersey 08016 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)	KINGSBURY, Celia
III-3-5	Address	1 Woodland Avenue Cream Ridge, New Jersey 08514 United States of America
III-3-6	State of nationality	NZ
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)	HO, Koc-Kan
III-4-5	Address	104 Pheasant Run Monmouth Junction, New Jersey 08852 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)	QUINTERO, Jorge
III-5-5	Address	7 Van Delft Drive South Amboy, New Jersey 08879 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)	YOU, Ming
III-6-5	Address	3 Madison Drive Plainsboro, New Jersey 08536 United States of America
III-6-6	State of nationality	CN
III-6-7	State of residence	US
III-7	**Applicant and/or inventor**	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	PARK, Haengsoon
III-7-5	Address	8910 Tamarron Drive Plainsboro, New Jersey 08536 United States of America
III-7-6	State of nationality	KR
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)	LU, Yingchun
III-8-5	Address	91 Stillwell Road Kendall Park, New Jersey 08824 United States of America
III-8-6	State of nationality	CN
III-8-7	State of residence	US
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	HANSEN, Philip
IV-1-2	Address	Heslin Rothenberg Farley & Mesiti P.C. 5 Columbia Circle Albany, New York 12203 United States of America
IV-1-3	Telephone No.	(518) 452-5600
IV-1-4	Facsimile No.	(518) 452-5579
IV-1-6	Agent's registration No.	32,700
IV-2	**Additional agent(s)**	additional agent(s) with same address as

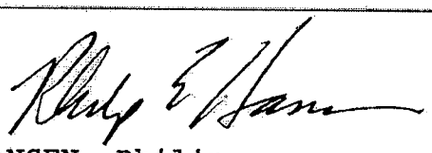
IV-2-1	Name(s)	first named agent TIMMER,Edward(46,248); ROTHENBERG,Jeff(26,429); BODEN,Martha(39,115)
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	05 April 2005 (05.04.2005)
VI-1-2	Number	60/668,286
VI-1-3	Country	US
VI-2	**Priority claim of earlier national application**	
VI-2-1	Filing date	15 November 2005 (15.11.2005)
VI-2-2	Number	60/736,663
VI-2-3	Country	US
VI-3	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)

VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
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	-	

PCT REQUEST

Original (for **SUBMISSION**)

449

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	199	-
IX-3	Claims	18	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	223	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	**Figure of the drawings which should accompany the abstract**		
IX-20	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**		
X-1-1	Name (LAST, First)	HANSEN, Philip	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-116002- -00000-0000

Fecha: 2007-11-01 16:29:37 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 449

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- ♦ Indicación de que se solicita la concesión de una patente [✓]
- ♦ Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- ♦ Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- ♦ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ♦ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- ♦ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- ♦ Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ♦ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Nova Cortes
Firma Responsable

Fecha_____

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